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HEALTH ASSESSMENT DOCUMENT FOR CADMIUM

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Prepared by

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16. ABSTRACT

This document provides a critical assessment of health effects and public health risks associated with environmental exposure to cadmium (Cd). Sources and routes of exposure are discussed and identified. Dose-effect/response relationships and populations at special risk are delineated.

Cadmium is naturally present in most environmental media. Major anthropogenic sources are: (1) smelting and mining, (2) certain manufacturing processes, and (3) waste disposal operations. Food is the largest environmental source for most humans, although Cd intake from smoking can equal or exceed Cd intake from food.

Acute non-lethal exposure is associated with chronic respiratory effects. However, since most environmental exposures to Cd are of a long-term, low-level type, primary emphasis has been placed on discussing effects of such chronic exposure. Cadmium's accumulation in the kidney results in renal tubular dysfunction after many years of exposure. Estimates of the concentration of Cd in the renal cortex necessary to induce these effects and estimates of exposure necessary to produce the critical renal concentration vary widely, partially due to individual biological variability. Populations at special risk to Cd are cigarette smokers, as well as the older segments of the population (>50 years of age).

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U.S. ENVIRONMENTAL PROTECTION AGENCY
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Research Triangle Park, N.C. 27711

i-a

PREFACE

This document deals with the various aspects of cadmium as an Air pollutant in accordance with Section 122(a) of the Clean Air Act as amended in August 1977. Section 122(a) requires that

> "Not later than one year after date of enactment of this section and after notice and opportunity for public hearing, the Administrator shall review all available relevant information and determine whether or not emissions of ... cadmium ... into the ambient air will cause, or contribute to, air pollution which may reasonably be anticipated to endanger public health."

If the Administrator does affirmatively decide that emissions of cadmium do endanger public health,

> "he shall simultaneously with such determination include such substance in the list published under section 108(a)(1) or 112(b)(1)(A) ..., or shall include each category of stationary sources limiting such substance in significant amounts in the list published under section 111(b)(1)(A), or take any combination of such actions."

This health assessment document is intended to serve as the basis for the Administrator's evaluation of cadmium as an air pollutant. While the preparation of this document has required a comprehensive review of current scientific knowledge regarding airborne cadmium, the references cited do not constitute a complete bibliography.

The Agency acknowledges the contributions of each individual who participated in the development of this document. However, the Environmental Protection Agency accepts full responsibility for the contents herein.

ABSTRACT

The purpose of the present document is to provide a critical assessment of health effects and potential risk to human health associated with environmental exposure to cadmium. In keeping with this objective, major current sources and routes of exposure are identified and discussed, as are key health effects associated with cadmium exposure. Furthermore, dose-effect and dose-response relationships are characterized and populations at special risk are delineated. Lastly, the potential impact of current and likely future exposure patterns on the health of the American public is discussed.

Cadmium is naturally present in trace amounts in most environmental media including soil, water, air, and food. Substantial additional amounts of the element are added to each of these media as a consequence of man's activities. Included among major anthropogenic sources are: (1) smelting and mining operations; (2) electroplating and certain other manufacturing operations; and (3) waste disposal operations, e.g., municipal incineration and land application of solid waste materials. Man is exposed to cadmium dissipated by each of these sources either directly through emissions into ambient air or water or indirectly via secondary deposition of the element on soils and subsequent uptake into the human food chain.

Food is presently the single largest environmental source of cadmium exposure for most humans. Current estimates indicate that daily dietary cadmium intake levels for most Americans vary from 10 to 50 μg/day. Cigarette smoking (one to three packs per day) can significantly increase cadmium intake in amounts equal to or exceeding that obtained from food. Ambient

air and drinking water generally contribute only small increments in cadmium uptake beyond that of food or cigarette smoking, except possibly in areas surrounding certain point sources that emit high levels of cadmium.

Two major types of adverse health effects of cadmium exposure can be distinguished--acute and chronic. Acute cadmium toxicity usually results from inhalation of cadmium at high-dose levels encountered in occupational settings. In cases of nonlethal inhalation exposure, chronic respiratory effects (pneumonitis) are of primary concern. In contrast, long-term, lower-level exposures to cadmium via air or other media, e.g., food, are of most concern because consequent accumulations of cadmium in the kidney can induce associated renal tubular dysfunction as the "critical effect" of chronic cadmium exposure.

The most accurate index of the effective internal cadmium dose necessary to induce renal dysfunction is the concentration of the metal in the renal cortex. The most common currently accepted value for the "critical concentration" of cadmium in the kidney is 200 μg/g wet weight of renal cortex. Estimates of external exposure levels sufficient to cause the critical renal cortex concentration to be reached vary considerably. For example, estimates of requisite ingestion levels derived from metabolic modeling approaches range from 200 to 480 μg/day. However, levels near the lower end of the range (ca. 200 μg/day) are presently accepted as the best estimates of "threshold" dietary intake levels typically needed to result in the critical renal cortex concentration being reached over a 50-year exposure period. Other approaches utilizing metabolic models, actual measures of dietary cadmium exposures and associated prevalence of renal dysfunction, suggest that wide variability may exist across human populations in regard to ingestion levels necessary to induce the critical effect and that a very small proportion of the most sensitive members of the general population might be affected at dietary levels somewhat below 200 µg/day.

Due to the accumulative nature of cadmium retention in the kidney, older members (i.e., over 40 to 50 years of age) of exposed populations typically have both the highest renal cortex concentrations of the metal and the highest prevalence of cadmium-induced renal dysfunction. Thus, older members of the United States population would be expected to be most immediately at risk for future increments in cadmium exposure. Also, due to increased absorption of cadmium being associated with certain nutritional deficiencies, e.g., insufficient levels of dietary iron, zinc, or calcium, older members of the population with such nutritional deficits are likely to be at even greater risk. Since everyone ages and is therefore subject to long-term renal cadmium accumulation, the entire United States population should be considered at potential risk for cadmium-induced renal dysfunction. Also, since smokers are exposed to and retain significantly higher levels of cadmium than non-smokers, they are clearly at greater risk than non-smokers for cadmium-induced adverse health effects.

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CONTENTS

Page

LIST OF FIGURES.. xii
LIST OF TABLES... xiii
ABSTRACT... iii

1. SUMMARY AND CONCLUSIONS.. 1-1
   1.1 INTRODUCTION... 1-1
   1.2 HEALTH ASPECTS OF CADMIUM IN MAN AND ANIMALS................. 1-4
      1.2.1 Metabolism of Cadmium in Man and Experimental Animals.... 1-5
      1.2.2 Biological and Adverse Health Effects in Man and Animals. 1-7
   1.3 EFFECTS OF CADMIUM ON HUMAN POPULATIONS...................... 1-13
   1.4 HUMAN HEALTH RISK ASSESSMENT OF CADMIUM...................... 1-17
      1.4.1 Introduction... 1-17
      1.4.2 Sources and Routes of Exposure........................... 1-18
      1.4.3 Human Population Responses to Cadmium in Human Risk Assessment.... 1-21
         1.4.3.1 Summary of human health effects of cadmium.......... 1-21
         1.4.3.2 Dose-effect/dose-response relationships of cadmium.. 1-22
         1.4.3.3 Populations at risk to the adverse health effects of cadmium.... 1-27
      1.4.4 Overall Conclusions...................................... 1-32

2. BIOLOGICAL SIGNIFICANCE AND ADVERSE HEALTH EFFECTS OF CADMIUM.... 2-1
   2.1 INTRODUCTION... 2-1
   2.2 METABOLISM OF CADMIUM.. 2-2
      2.2.1 Sources of Exposure...................................... 2-2
      2.2.2 Inhalation... 2-3
      2.2.3 Gastrointestinal Absorption.............................. 2-4
      2.2.4 Other Absorption Routes.................................. 2-4
      2.2.5 Transport and Deposition................................. 2-4
      2.2.6 Excretion.. 2-6
   2.3 SUB-CELLULAR AND CELLULAR ASPECTS OF CADMIUM TOXICITY........ 2-7
      2.3.1 General Sub-Cellular Effects............................. 2-7
      2.3.2 Metallothionein.. 2-22
   2.4 RESPIRATORY EFFECTS OF CADMIUM............................... 2-27
      2.4.1 Effects on Humans.. 2-27
      2.4.2 Animal Studies... 2-29
   2.5 RENAL EFFECTS OF CADMIUM..................................... 2-32
      2.5.1 Animal Studies... 2-33
      2.5.2 Human Studies.. 2-37
   2.6 THE CARDIOVASCULAR SYSTEM.................................... 2-41
      2.6.1 Animal Studies... 2-41
      2.6.2 Human Hypertension....................................... 2-44

Page

2.7 EFFECTS OF CADMIUM ON REPRODUCTION AND DEVELOPMENT.......... 2-44
  2.7.1 Testicular Effects.......... 2-44
  2.7.2 Ovarian Effects.......... 2-54
  2.7.3 Embryotoxic and Teratogenic Effects.......... 2-55
2.8 ENDOCRINE EFFECTS OF CADMIUM.......... 2-70
  2.8.1 Gonadal Effects.......... 2-71
  2.8.2 Pancreatic Effects.......... 2-71
  2.8.3 Adrenal Effects.......... 2-73
  2.8.4 Thyroid Effects.......... 2-75
  2.8.5 Pituitary Effects.......... 2-76
2.9 EFFECTS OF CADMIUM ON BONE AND MINERAL METABOLISM.......... 2-76
  2.9.1 Animal Studies.......... 2-77
  2.9.2 Human Aspects.......... 2-78
2.10 HEPATIC EFFECTS OF CADMIUM.......... 2-78
  2.10.1 Animal Studies.......... 2-79
  2.10.2 Human Aspects.......... 2-80
2.11 NEUROLOGICAL EFFECTS OF CADMIUM.......... 2-81
2.12 GASTROINTESTINAL EFFECTS OF CADMIUM.......... 2-85
2.13 HEMATOLOGICAL EFFECTS OF CADMIUM.......... 2-86
2.14 IMMUNOSUPPRESSIVE EFFECTS OF CADMIUM.......... 2-88
2.15 MUTAGENIC AND CARCINOGENIC EFFECTS OF CADMIUM.......... 2-90
  2.15.1 Mutagenic Effects of Cadmium.......... 2-91
  2.15.2 Tumorigenic Cadmium Effects in Animals.......... 2-94
  2.15.3 Human Carcinogenesis Studies.......... 2-100
2.16 INTERACTIONS OF CADMIUM WITH OTHER METABOLIC FACTORS.......... 2-103
  2.16.1 Zinc.......... 2-103
  2.16.2 Selenium.......... 2-104
  2.16.3 Calcium.......... 2-107
  2.16.4 Iron.......... 2-107
  2.16.5 Cooper.......... 2-108
2.17 REFERENCES FOR CHAPTER 2.......... 2-110

3. HUMAN EPIDEMIOLOGY.......... 3-1
3.1 INTRODUCTION.......... 3-1
3.2 CADMIUM IN BLOOD AND URINE OF HUMAN POPULATIONS.......... 3-2
  3.2.1 Sources of Variations in Human Blood Cadmium Levels.......... 3-3
    3.2.1.1 Demographic variability in human blood cadmium levels.......... 3-4
    3.2.1.2 Other variation.......... 3-14
    3.2.1.3 Occupational exposure and blood cadmium.......... 3-14
  3.2.2 Sources of Variation in Human Urine Cadmium Levels.......... 3-15
  3.2.3 Sources of Cadmium Variation in Human Hair.......... 3-20
3.3 RESULTS OF AUTOPSY STUDIES.......... 3-22
3.4 EPIDEMIOLOGICAL STUDIES OF CADMIUM EXPOSURE IN JAPAN.......... 3-33

Page

3.4.1 Itai-Itai Disease Studies........................ 3-35
3.4.2 Epidemiological Studies of Other Cadmium-Polluted Areas in Japan...................... 3-38
3.5 EPIDEMIOLOGY OF CADMIUM, HYPERTENSION, AND CARDIOVASCULAR DISEASES.................................. 3-41
3.6 EPIDEMIOLOGICAL STUDIES OF THE RESPIRATORY TRACT....... 3-43
3.7 CADMIUM AND CANCER..................................... 3-44
3.8 EPIDEMIOLOGICAL STUDIES RELATING TO CHROMOSOMAL ABNORMALITIES.. 3-48
3.9 EPIDEMIOLOGICAL STUDIES OF OCCUPATIONAL EXPOSURE TO CADMIUM... 3-49
3.10 REFERENCES FOR CHAPTER 3............................... 3-50

4. HUMAN HEALTH RISK ASSESSMENT OF CADMIUM..................... 4-1
4.1 INTRODUCTION... 4-1
4.2 EXPOSURE ASPECTS....................................... 4-4
4.2.1 Ambient-Air Levels of Cadmium.................. 4-5
4.2.2 Drinking Water................................. 4-13
4.2.3 Soils... 4-15
4.2.4 Food.. 4-20
4.2.5 Other Sources.................................. 4-37
4.3 HEALTH EFFECTS SUMMARY................................ 4-39
4.4 DOSE-EFFECT AND DOSE-RESPONSE RELATIONSHIPS OF CADMIUM IN HUMANS................................ 4-43
4.4.1 Dose Aspects.................................. 4-43
4.4.2 Dose-Effect/Dose-Response Aspects.............. 4-45
4.5 POPULATIONS AT RISK TO EFFECTS OF CADMIUM.............. 4-61
4.6 UNITED STATES POPULATION GROUPS IN RELATION TO PROBABLE CADMIUM EXPOSURES............................ 4-73
4.7 REFERENCES FOR CHAPTER 4............................... 4-83

APPENDIX A.. A-1

FIGURES

Number · Page

3-1. Distribution of mean urine cadmium concentrations by age..... 3-18
3-2. Geometric and arithmetic means of cadmium concentration in kidney cortex are shown for each decade of life.......... 3-25
3-3. Cadmium in whole kidney tissues and its relationship to age.. 3-26
4-1. Diagrammatic representation of multi-media routes by which cadmium exposure of man can occur after dissipation of the element into the environment by anthropogenic activities.. 4-6
4-2. Trends in 50th percentile of annual averages for cadmium associated with metal industry sources at urban sites.. 4-11
4-3. Contribution of food groups to cadmium intake................ 4-27
4-4. Effects of soil pH on cadmium uptake by vegetables.......... 4-32
4-5. Calculated (lines) and observed (symbols o, o, *) dose-response relationships for cadmium-induced increase (>97.5) percentile of reference group) of urinary β_2-microglobulin excretion. 4-55
4-6. Regions used in cadmium analysis............................ 4-80

TABLES

Number Page

1-1. Cadmium exposure required for reaching a kidney cortex concentration of 200 μg Cd/g using different alternatives for biological half-time in kidney cortex and exposure time.. 1-23
1-2. Media contributions to normal retention of cadmium..... 1-24
1-3. Estimated relative contribution of dietary intake, cigarette smoking and ambient air cadmium levels of total cadmium retention from all sources.............. 1-31
1-4. Average exposure and number of people exposed to annual air cadmium levels greater than 0.1 ng/m^3 by specified source types.. 1-33
2-1. Sub-cellular and cellular cadmium toxicity in experimental animals...................................... 2-9
2-2. Species variations in susceptibility to cadmium-induced testicular necrosis................................. 2-47
2-3. Cadmium in placentas and fetuses...................... 2-65
2-4. Placental to maternal blood concentration ratios....... 2-66
2-5. Placental to fetal cadmium concentration ratios........ 2-67
2-6. Effects of maternal dietary cadmium (17.2 μg/ml), given during gestation, on body weights and body trace metals of neonates.. 2-69
2-7. Summary of mutagenicity test results.................. 2-92
2-8. Studies on cadmium tumorigenesis in experimental animals.. 2-96
2-9. Summary of results of human epidemiologic studies of cancer effects associated with occupational exposures to cadmium... 2-101
3-1. "Normal" blood cadmium levels.......................... 3-7
3-2. "Normal" urine cadmium levels.......................... 3-16
3-3. Urine cadmium levels for "normal" males in Dallas, Texas, determined by atomic absorption.............. 3-19
3-4. Cadmium in human liver................................. 3-24
3-5. Cadmium concentration in human renal cortex by age: means and 99% level of significance................. 3-27
3-6. Age group means and standard deviations for tissue cadmium... 3-27
3-7. Mean cadmium values related to place of residence...... 3-29
3-8. The average cadmium concentrations in tissues examined (geometric means and medians), the ranges and the number of samples above the detection limit/number of samples in each age group; both sexes are included, with total number of subjects for each age group indicated in parentheses... 3-30
3-9. Cadmium in the kidney cortex of U.S. adult population.. 3-33

Number Page

4-1. Annual average urban atmospheric cadmium concentrations reported by National Air Surveillance Networks, 1970-1974 4-8
4-2. Cadmium in soils 4-16
4-3. Concentrations of cadmium in urban and suburban soils - 1972 4-17
4-4. Cadmium content in different food categories in the U.S.A 4-22
4-5. Cadmium content of selected adult foods 4-24
4-6. Food groups by mean cadmium content and their contribution to daily cadmium intake 4-25
4-7. Cadmium intake of teen-age males by food class 4-26
4-8. Distribution of daily dietary cadmium intake (μg/day) of U.S. populations as determined by fecal excretion studies 4-29
4-9. Cadmium content of several crops and tissues as a function of cadmium loading of soil 4-31
4-10. Cadmium content of soils and crops grown on acid and limed sludged sites 4-34
4-11. Media contributions to normal retention of cadmium 4-38
4-12. Cadmium exposure required for reaching a kidney cortex concentration of 200 μg Cd/g using different alternatives for biological half-time in kidney cortex and exposure time 4-49
4-13. Prevalence of tubular proteinuria and suspected patients among adults more than 50 years of age in relation to village average rice cadmium concentrations 4-59
4-14. Prevalence of tubular proteinuria in relation to age and village average rice cadmium concentation.. 4-60
4-15. Relative contribution of cigarette smoking to total daily cadmium retention 4-65
4-16. Estimated relative contribution of dietary intake, cigarette smoking, and ambient air cadmium levels to total daily cadmium retention from all sources 4-67
4-17. Percentage of critical daily cadmium retention level yielding renal dysfunction achieved by smokers as a function of ambient air cadmium levels 4-69
4-18. Average exposure and number of people exposed to annual air cadmium levels greater than 0.1 ng/m^3 by specified source types 4-75
4-19. Estimate of cumulative population exposed to specified cadmium concentrations from municipal incinerators 4-76
4-20 Estimate of cumulative population exposed to specified cadmium concentrations from iron and steel mills 4-77
4-21. Estimated population exposed to specified levels from primary smelters 4-78
4-22 Estimate of population exposed to specified levels from secondary smelters 4-79
4-23. Number of births by race and size of population 4-81

1. SUMMARY AND CONCLUSIONS

1.1 INTRODUCTION

The purpose of the present document is to evaluate the toxic effects of cadmium in man and animals and to assess the potential risk to human health associated with environmental exposure to that element. This chapter summarizes the main issues addressed in the document, the most important evidence bearing on these issues, and major conclusions based on the evidence discussed.

Among the issues addressed in the document are the following points of primary concern:

(1) Can demonstrable adverse human health effects presently be associated with exposure to cadmium; and are such health effects reversible or irreversible? Of particular interest is whether cadmium induces sufficiently deleterious effects on human health or welfare to warrant its classification as a "hazardous air pollutant?"

(2) What are the major sources of cadmium exposure in human populations, especially among Americans, and what are the most important routes of exposure that currently exist? Can the relative contributions of different sources and routes of exposure to uptake and retention of the element in the general population be estimated? If so, with what degree of confidence? Related to this is the issue of sensitivity and accuracy of existing measurement methodology for determining levels of cadmium in tissue matrices and nonbiological materials.

(3) Based on known exposure information and taking into account other interacting factors, can particular human populations be identified as being

at special risk for adverse health effects due to cadmium exposure? If so, under what circumstances and in what numbers are the members of those populations expected to be at unacceptable risk?

No exhaustive compilation of the extensive currently available literature on the toxicity of cadmium is provided. Rather, a much more selective review and evaluation of the pertinent literature related to the above points of concern is presented. The evaluation of toxic effects of cadmium in animals and man is based upon (1) studies of cadmium intoxication in experimental animal models and (2) human epidemiological and clinical research. In addition, in assessing the potential risk to human health associated with exposure to cadmium, major sources of cadmium exposure are identified, and their present relative contributions to human intake and retention of the metal are estimated, dose-effect and dose-response relationships for the occurrence of certain crucial health effects are defined, and the levels of cadmium retention at which such "critical effects" of acute and chronic exposure occur are indicated. Estimations are also made of multimedia cadmium exposure levels necessary to achieve sufficient retention of the metal for induction of the critical effects of chronic exposure. Lastly, populations at special risk for exhibiting critical adverse health effects are delineated according to particular factors that place them at greater risk than others, and projections are made regarding numbers of such people likely to be adversely affected by excessive environmental exposure to cadmium.

Several points of concern from a public health standpoint emerge from the present analysis. One is that cadmium appears to be somewhat unique among the elements exerting toxic effects on man and other living organisms in that: (1) its half-time in the body is unusually long, sufficiently long that active accumulation of the element occurs over most of the lifetime of man; (2) its accumulation does not include major deposition as an "inert" fraction in bone, as is the case with lead, but rather it is lodged in soft tissue, chiefly the kidney; and (3) its consequent adverse health effects, especially where clinically manifest, appear to be essentially irreversible.

Another matter of concern is that large numbers of the general American population appear to be regularly exposed to cadmium from many sources, but mainly food, and that retention levels are such that only a relatively small natural margin of safety likely exists for some individuals. Thus, any additional cadmium accumulation over a long period of time may approach levels sufficient to cause adverse health effects in significant segments of the United States population. Of particular concern in that regard is the fact that cigarette smoking contributes very significant amounts of cadmium to body levels, at times equivalent to or more than that derived from food, thus placing millions of existing and future smokers at special risk.

At present, the major anthropogenic sources contributing to environmental exposures to cadmium are: (1) municipal incinerators; (2) iron and steel mills; (3) primary copper, lead, zinc and cadmium smelters; and (4) secondary zinc and cadmium smelters. Ambient air concentrations resulting from emissions from most of these sources currently do not appear to pose much risk to the general population; however, emission levels are such in some cases that significant increases in cadmium body burden might be expected for individuals residing near certain of the types of sources listed and these individuals may be at risk to ultimately manifest cadmium-induced renal dysfunction.

Also of some concern are projections that can reasonably be made regarding certain developments that could potentially increase hazards from cadmium exposure in the future, if adequate safeguards or regulatory controls are not implemented. More specifically, although present exposures to existing levels of atmospheric cadmium generally do not now appear to pose much risk to most Americans, two developments may substantially increase ambient air levels of cadmium, i.e.: (1) expanded municipal incineration of high-cadmium content sewage sludge or other waste materials; and (2) expanded fossil fuel use, especially anticipated large increases in coal burning at coal-fired power plants. Increased ambient air cadmium levels from the above sources, if not adequately controlled, would not only pose greater health risks via increased cadmium exposure through direct inhalation, but would also be expected to increase levels of cadmium ingested in food and water via secondary deposition of airborne particles on agricultural land and water. Other developments which could more directly impact on amounts of cadmium introduced into the human food chain are: (1) increased landspreading of cadmium-containing sewage sludge or other waste materials on agricultural land used for growing food crops; and (2) expanded use of cadmium-contaminated phosphate fertilizers on agricultural land. Except in the case of the latter use of phosphate fertilizers, current or anticipated EPA regulations are expected to provide adequate control of cadmium entry into the environment from the above sources.

1.2 HEALTH ASPECTS OF CADMIUM IN MAN AND ANIMALS

A variety of biological and adverse health effects have been documented in experimental animals and man under conditions of acute and chronic cadmium exposure. It should be noted that, as far as can best be determined, cadmium plays no beneficial or essential role in the health of man or animals. In view of this, demonstrated biological and adverse health effects of this particular element must be considered in the absence of any health benefit--health cost balance.

1.2.1 Metabolism of Cadmium in Man and Experimental Animals

Cadmium, like other multi-media environmental contaminants, may be introduced into the target organism from a number of sources, including air, food, and water. The relative amount of cadmium inhaled and absorbed via the pulmonary tract depends on the physiochemical character of the form of airborne cadmium as well as subsequent fate of the cadmium deposited in the respiratory tract. More specifically, the extent of deposition in the pulmonary tract is a function of particle size and solubility. Deposition in lung is about 50 percent for particles of 0.1 micrometer mean mass diameter (MMD) decreasing to about 10 percent for particles of 5.0 micrometers MMD. Systemic absorption of the amount deposited in the respiratory tract of man is estimated to be from 20 to 25 percent of the deposited fraction. The amount of cadmium absorbed from inhalation of cigarette smoke, however, appears to be significantly higher.

Since human populations generally acquire most of their cadmium from dietary intake, gastrointestinal absorption is the major route of entry of cadmium into man. About 5 to 6 percent of the cadmium entering the gastrointestinal tract is absorbed; based on clinical and epidemiological observations, however, nutritional deficiencies such as low calcium and iron can markedly increase this figure.

Blood is the vehicle for transport of cadmium absorbed via inhalation or ingestion. Cadmium is then taken up from the blood into the liver, where incorporation into metallothionein occurs, followed by release into blood and deposition of cadmium-thionein in the kidney. In populations with minimal exposure to cadmium, about half of the organ distribution of cadmium is in the liver and kidneys, with the kidneys accounting for about one-third of the total body burden. Other organs accumulating cadmium include the testes, lungs, pancreas, spleen, and various endocrine organs. In contrast, cadmium concentration in bone, brain, and muscle tissue is very low. However, despite low concentrations in muscle, due to the large mass of muscle tissue, a large part of the overall body burden exists in muscle tissue.

The half-time of cadmium in the body, a measure of its retention or accumulation, has been calculated to be 18 to 38 years. Whereas little cadmium is typically found in man at birth, a steady accumulation of the element occurs up to about 50 years of age, with a very large portion of the accumulating cadmium being retained in soft tissue such as the kidney. Beyond 50 years of age, the levels of renal cadmium usually reach an asymptotic level and remain essentially constant or decrease.

Cadmium is excreted mainly via the urinary and gastrointestinal tracts; daily urinary excretion is less than 1 μg in the non-smoking population. Cadmium exposure from whatever source tends to increase the daily urinary output of the element. Biliary excretion occurs in animals but has not yet been demonstrated to be significant in man.

The transport and toxicity of cadmium are intimately associated with an inducible metal-binding protein, metallothionein, which binds cadmium, zinc, and certain other divalent metal ions. On absorption, cadmium is transported via blood to the liver where it is incorporated into metallothionein. The protein-bound cadmium is then released back into the blood and undergoes deposition in the kidney and other soft tissues. The binding of cadmium by metallothionein and the deposition or synthesis of the complex in kidney and other soft tissue apparently accounts for its very long half-time in the body. Such binding initially results in protection against toxic effects potentially exerted by unbound free cadmium; however, once metallothionein binding and storage mechanisms are saturated under conditions of prolonged cadmium exposure, the presence and release of metallothionein-complexed cadmium can result in substantial toxic effects. Thus, for example, nephrotoxic effects of cadmium are a consequence of its mode of transport to and long-term deposition in the kidney in a form complexed with metallothionein.

Acquisition of data on the uptake, deposition in body tissues, and excretion of cadmium has been achieved through the use of sensitive measurement techniques for the detection of the element in biological tissues. A number of methods are presently available which, when employed in competent laboratories and using good quality control, can reliably measure cadmium at ultra-trace levels (i.e., at ng/g or ng/m^3 concentrations). At present, atomic absorption spectrometry appears to be the most satisfactory analytical approach for assessing cadmium levels in media of interest for human health evaluations, e.g., urine, blood and tissue levels, as well as in air and foodstuffs. Details of specific analyses used in particular studies involving biological media are included in portions of the Human Epidemiology Chapter (Chapter 3).

1.2.2 Biological and Adverse Health Effects in Man and Animals

Extensive information exists on the acute and chronic effects of cadmium in man and experimental animals. Much of the data on animals, however, is derived from studies utilizing relatively high exposures to cadmium administered by direct systemic injections of the metal; such data, while often of questionable environmental relevance, are valuable in delineating the upper range of toxicological effects in a number of organ systems. Also, once high exposure effects have been demonstrated, follow-up studies have been conducted in some cases to define dose-effect relationships at much lower levels of exposure and, at times, by means of inhalation or oral routes of exposure.

Adverse health effects observed in experimental animals exposed to high cadmium levels include serious acute or chronic damage to several organ systems. Among the more dramatic types of high exposure effects are morphological or functional signs of: renal damage, testicular necrosis, injury of the pulmonary tract, embryotoxic and teratogenic responses, endocrine system derangement, experimental hypertension and related cardiovascular responses, anemia, hepatotoxicity, carcinogenesis and mutagenesis, and reduced immunological responses. Such effects have been most consistently demonstrated to occur after single intraperitoneal or subcutaneous injections of various cadmium salts in solution and at dose levels exceeding 0.5 to 1.0 mg Cd/kg body weight.

Only a few of the above types of damage, usually of much reduced severity, have been produced in experimental animals with lower, chronic cadmium exposures. Probably the most typical and severe effect of chronic low level cadmium exposure is renal dysfunction. More specifically, cadmium affects the reabsorption capacity of the proximal tubules in the kidney, initially inducing increased urinary excretion of low molecular weight proteins. Thus, tubular proteinuria is one of the earliest signs of chronic cadmium intoxication. Progressively more severe damage to the kidney results from continued exposure, producing aminoaciduria, glucosuria and phosphaturia as later signs of more advanced renal damage. Significant morphological changes accompany these biochemical signs of renal dysfunction and include:

diffuse scarring of peritubular capillaries, interstitial edema, adhesions between Bowman's capsule and glomerular capillaries, and tubular atrophy. One or more of these functional and morphological signs of renal damage have been observed in rats and rabbits with prolonged oral exposure to cadmium over periods of weeks or months, starting at exposure levels of 2 ppm or 10 ppm in the drinking water. Kidney cortex cadmium levels at which definite signs of severe kidney damage are observed in animals have been reported to fall in the range of 150 to 450 μg Cd/g wet weight.

Additional health effects have been observed in animals with long-term exposure to cadmium. For example, significant reductions in birth weights have been reported for offspring born to female rats exposed via inhalation to cadmium sulfate (at 3 mg/m^3) for seven months or to cadmium chloride in the diet (at 200 ppm). The reductions in birth weights appear to result from cadmium effects on maternal and fetal nutritional status and likely occur secondarily to reductions in fetal copper, iron and zinc levels.

Significant immune suppression effects have also been observed with oral exposures of mice and rabbits to cadmium chloride in drinking water (at levels of 10 ppm in that medium) for periods of 5 to 10 weeks. Such immune suppression effects have been observed in the absence of other more classic signs of cadmium toxicity, e.g., indications of renal damage, and may represent heretofore unrecognized "subclinical" effects of chronic cadmium exposure. Some experimental evidence suggests that immune suppresssion effects may at times persist beyond the cessation of exposure to cadmium.

The literature relevant to man deals with both acute and chronic health effects arising from cadmium exposure. Much of the data is derived from occupational settings and responses of populations residing in geographic areas of demonstrated high cadmium pollution.

In human beings, acute effects of cadmium generally result from occupational exposure via inhalation. The chief clinical feature of acute cadmium inhalation exposure is pneumonitis, i.e., pulmonary congestion and edema. Individuals who survive this acute episode regain partial lung function but appear to have a higher probability of subsequently dying of chronic pulmonary insufficiency. The inhalation of approximately 1 mg/m^3 of cadmium over an 8 hour period gives rise to clinically evident symptoms in sensitive individuals, whereas an air level of 5 mg/m^3 inhaled over the same time period can be lethal. At much lower air exposure levels, in the range of 1 to 100 ng/m^3, no acute exposure effects appear to occur. Rather, the main risk associated with such air levels arises from secondary contamination of water or soils that may increase cadmium levels entering the human food chain.

Chronic adverse health effects of cadmium in man consist chiefly of effects on the renal system and the respiratory tract. The renal effects have been well documented as a systemic index of toxicity outside of occupational settings; chronic respiratory effects, in contrast, are mainly seen in cadmium workers who experience long, steady exposure to the element. The kidney is therefore generally considered to be the main target organ affected by chronic cadmium exposure, with renal dysfunction typically viewed as the "critical effect." The renal dysfunction is specifically manifested in terms of tubular proteinuria at first, followed by aminoaciduria, glycosuria, and other signs of more severe kidney damage if exposure is continued at the same level.

Cadmium-induced tubular proteinuria can be recognized by the elevated excretion of the protein β_2-microglobulin, and a number of studies have shown that this protein is elevated many-fold in cases where cadmium played a clear-cut role in renal dysfunction. It has been demonstrated that the prevalence of proteinuria increases as a function of duration of cadmium exposure.

Disturbances in kidney function also exert their effects on bone and mineral metabolism, via effects on calcium and phosphorus, extreme examples of which are osteoporosis and osteomalacia. Itai-Itai or "Ouch-Ouch" disease, observed in Japan is essentially renal tubular dysfunction with osteoporosis and osteomalacia. Additional secondary effects of renal dysfunction are kidney stones, observed in Swedish workers exposed to cadmium; and osteomalacia, in French workers.

It should be emphasized that, once renal tubular dysfunction has proceeded to the point of pronounced proteinuria, it is essentially irreversible. Also, there is considerable evidence, both from human and animal studies, that such irreversible damage typically occurs when cadmium levels in the kidney cortex exceed approximately 200 μg/g wet weight, especially under conditions of continued exposure (see Risk Assessment Summary).

The chief chronic pulmonary effect of cadmium appears to be centrolobular emphysema and bronchitis resulting from several years of occupational exposure to cadmium oxide fumes, cadmium oxide dust, and cadmium pigment dust. Lung impairment is possible at cadmium oxide fume levels below 100 $\mu g/m^3$ of work place air, depending upon exposure time.

As for other health effects, although hypertension has been demonstrated in laboratory animals chronically exposed through the diet, there is presently no conclusive evidence that cadmium is an etiological factor in human hypertension. In addition, only a few effects on the hematopoietic system, chiefly anemia of the iron-deficiency type, have been noted in man, usually under conditions of occupational exposure to cadmium.

At present, few data are available concerning the direct effects of cadmium on human reproduction and development; the few existing data, however, are consistent with results from animal experiments that have yielded evidence of significant reductions in birth weights as a consistent finding after oral exposures of pregnant animals. Apparently, based on human and animal tissue analysis, little cadmium crosses the transplacental barrier *per se*; however, animal studies have shown that cadmium exposure during pregnancy has an effect on zinc and copper levels in the newborn, probably indirectly due to nutritional deficits, such as zinc deficiency, induced by cadmium. Lastly, although teratogenic effects have been demonstrated in animals at high exposure levels, no evidence has yet been advanced for cadmium being a human teratogen.

In regard to possible mutagenic effects of cadmium, some mutagenic effects in animals have been reported to occur with systemic injections of high doses of cadmium or in *in vitro* test systems; but no data are available that demonstrate mutagenic effects with either oral or inhalation exposure of animals. As for the little available data on mutagenicity in man, particularly with long-term exposure, the findings reported are contradictory and no firm conclusions can be reached at this time. The case for cadmium being carcinogenic in animals is supported only by data on tumorogenic effects induced at high exposure levels achieved via systemic injections. As for carcinogenic effects in man, some evidence suggests that heavily-exposed industrial workers may be at higher risk for prostatic cancer; but that evidence is not conclusive. Also, some data show a correlation between cadmium in drinking water and cancer incidence in large geographic areas, but this data is confounded by the presence of other potentially carcinogenic metals and smoking.

As indicated above, several well established health effects of cadmium, e.g., renal dysfunction and its secondary consequences, have been shown to be essentially irreversible and can exert a significant negative impact on the health and well-being of humans. Furthermore, there is no medical treatment presently available that can prevent the accumulation of cadmium in the kidney or achieve elimination or reduction of cadmium stored in the kidney or other soft tissues. Thus, minimization of exposure to cadmium is the only effective approach currently available for averting its adverse health effects.

1.3 EFFECTS OF CADMIUM ON HUMAN POPULATIONS

Studies of various population groups that directly relate cadmium exposure to human health effects are required to define the levels of exposure at which the particular population groups demonstrate adverse health effects and to identify the specific population segments at high risk. At present, only occupationally exposed workers and some population segments residing in areas of high cadmium exposure in Japan have been extensively studied. Using data from these and other studies, a chain of relationships can be defined from exposure to absorption and retention levels to adverse health effects for human populations. This can be done by (1) examining the distribution of cadmium sources to which humans are exposed; (2) assessing the levels of cadmium in blood, urine or soft tissues in various human population segments; and (3) correlating these findings with other research demonstrating adverse health effects at various cadmium levels in human tissue.

A number of studies have measured blood, urine, and hair cadmium levels as a function of demographic variability. When considering the relative validity of these studies, it is important to keep in mind the accuracy and precision of the methodology used for measuring cadmium levels. Some methods appear to be more subject to analytical error than others and, in the course of evaluating data at variance with the literature at large, it becomes apparent that at least part of the difficulty arises from deficient cadmium analyses.

"Average" cadmium blood values for the general (non-smoking) population in the United States and elsewhere are typically 1.0 μg Cd/dl whole blood or less, while occupational groups usually exhibit considerably higher values. Unfortunately, little data presently exist that clearly relate age, sex, and race to human blood cadmium levels. For example, no obvious age gradient is discernible among children's blood cadmium values, unlike the case with blood lead levels. In contrast, a clear relationship does exist between smoking status and blood cadmium levels. That is, it has been shown that adult blood cadmium values are invariably higher in the case of smokers. This finding has significance as one indication of smokers being at special risk for cadmium exposure.

It should be noted that blood cadmium values are generally a relatively poor index of chronic cadmium exposure and body accumulation, but rather are best used as indicators of recent or current high exposures. Urinary cadmium levels, on the other hand, appear to be reasonably good indicators of chronic low level cadmium exposure and body accumulation. In relation to that, regardless of the population groups studied, the urinary excretion of cadmium is seen to be age-dependent, increasing up to about 50 years of age, and then declining. The mean urine cadmium values from various studies generally indicate normal daily urine cadmium excretion levels to be from <1 to 2 μg Cd/day.

A number of studies have evaluated levels of cadmium in hair as an indication of exposure. Some question exists, however, as to the relevance of hair cadmium values in the case of studying general populations with low exposure to cadmium. Also, a number of analytical problems exist with hair analysis, including the problem of external contamination. Since a number of studies have shown no association between hair cadmium levels and the exposure status of their population groups, the utility of hair cadmium levels remains to be demonstrated.

Autopsy studies of cadmium levels in various human tissues have proven valuable in assessing levels of the element in key organs and total body burden. Such studies are of two types: case studies concerned with specific diseases and general population studies. Such studies have shown that cadmium levels in human kidney and liver increase with age. The values in liver decrease after 60 to 70 years of age, and kidney values level off after 50 years of age. Smokers show higher cadmium levels in organs than non-smokers. As a function of age, kidney values range from 5 μg/g wet weight in the first decade of life up to 100 or more μg/g at 50 years of age; mean values for adults are generally 20 to 40 μg/g. Smoking adds to the renal cadmium burden up to 50 percent or more above the corresponding values of non-smokers. Liver values increase from about 0.2 μg/g wet weight in the first decade of life up to 1.0 μg/g or more at age 70. Smoking also appears to increase liver cadmium values, particularly in the later decades of life.

A number of epidemiologic studies have dealt with areas of high cadmium exposure in Japan, including the main "Itai-Itai" belt area. Such studies identified Itai-Itai disease as a trio of symptoms--renal dysfunction with osteomalacia and osteoporosis--resulting from high cadmium exposure of people with a history of calcium and vitamin D deficiencies. Other areas of Japan having increased cadmium exposures were also studied, with particular reference to the prevalence of proteinuria. Collectively, these studies show that in high-cadmium areas significant numbers of the inhabitants have tubular proteinuria, with such renal derangement increasing with the age of the individuals and the time of residence in areas of high cadmium exposure.

The Japanese experience with Itai-Itai disease is an informative example of the potential widespread health problems that can ultimately result from cadmium contamination of the human food chain via deposition in water and soils used for agricultural purposes. The problem of detecting and coping with continuous cadmium exposure is well demonstrated by the late appearance of osteomalacia seen in Itai-Itai disease only after several decades of exposure. The Japanese experience also illustrates the difficulty in ending cadmium exposures due to heavy contamination of agricultural land, as noted in Chapter 4.

In regard to other cadmium health effects possibly being associated with exposure of specific population groups, the epidemiologic evidence for human hypertension and other cardiovascular diseases does not conclusively implicate any etiological role for cadmium. In particular, investigators who have controlled for smoking status have not shown an independent association between cadmium levels and hypertension. Also, studies focusing on the role of cadmium in producing chronic diseases of the lung other than cancer have virtually all centered on occupational groups and provide few data clearly demonstrating such effects in the general population. More specifically, although autopsy data have shown cadmium levels in tissue to be higher in persons with a diagnosis of emphysema, smoking status has not been controlled for as a confounding factor. Similarly, epidemiologic evidence often cited as implicating cadmium in the induction of prostatic or other cancers in human populations, while suggestive at this time, is not sufficiently strong so as to conclusively establish that the metal exerts carcinogenic effects on humans.

1.4 HUMAN HEALTH RISK ASSESSMENT OF CADMIUM

1.4.1 Introduction

Summarized above is our current knowledge concerning the biological and adverse health effects of cadmium in man and experimental animals, drawing on both clinical and epidemiological studies. This information, along with consideration of exposure aspects, is integrated in the last chapter of the present document in order to address the broader issue of risk to public health in the United States posed by cadmium exposure.

Two aspects of such a risk assessment must be considered: exposure aspects and population response. Key questions that must be addressed for exposure considerations include: (1) what are the environmental sources of cadmium in the United States; and, (2) what are the various routes by which cadmium enters the body? In regard to population health aspects, several additional questions must be considered: (1) What are the human biological and pathophysiological responses to cadmium? (2) Do there exist within the general population in the United States or elsewhere certain sub-groups at special risk to the adverse health effects of cadmium? (3) Quantitatively, what is the magnitude of the risk in terms of numbers of individuals potentially exposed to cadmium levels sufficient to induce particular adverse health effects?

1.4.2 Sources and Routes of Exposure

Trace amounts of cadmium are widely distributed naturally in the environment. Much higher amounts of the metal enter the environment, however, as a result of the manufacture, use, or disposal of cadmium-containing products or in the form of contaminants of other substances. Since virtually no recycling of the element occurs, its use is said to be dissipative, i.e., the amount entering the environment equals the amount produced or used. The current amount of cadmium entering the environment yearly in the United States ranges from 2,000 to 5,000 tons. Dissipation of cadmium in the general environment occurs via contamination of air, water and soil.

Ambient air levels of cadmium across the United States are usually in the range of nanograms per cubic meter (ng/m^3); however, much higher ambient air values, around 0.1 to 1.0 $\mu g/m^3$ (100 to 1000 ng/m^3), are at times found in regions of high cadmium production and industrial use. This may be compared to work place levels of about 50 to 100 $\mu g/m^3$ of cadmium in air associated with the induction of chronic health effects in cadmium workers. Airborne cadmium, in addition to being inhaled, may contribute to human exposure via secondary contamination of water and soil due to fallout and entry into the human foodchain. A matter of potential long-range concern in this regard is that future increased fossil fuel use could lead to higher ambient air cadmium levels and, indirectly through soil contamination, to increased cadmium in food crops.

Significant human exposure from cadmium-contaminated water supplies has occurred in some areas of the world, e.g., Japan; and certain waterways in the United States are contaminated with notable amounts of cadmium. Sources of drinking water in the United States, however, generally are not contaminated; in fact extensive surveys of the drinking water supplies of a large number of areas within the United States indicate that the vast majority of these supplies have cadmium levels below the recommended Public Health Service value of 10 parts per billion (ppb) (10 μg/1). It would be desirable, however, to determine whether any contamination of drinking water by cadmium occurs from supply distribution systems, particularly household plumbing.

In soils, cadmium levels reflect geochemical and anthropogenic sources. Man's activities add substantial cadmium to agricultural soils not only via fallout from the air or contamination of irrigation water, but also through intentional application of phosphate fertilizer and the increasing use of sewage sludge on agricultural land. Background soil levels in rural areas are normally of the order of 0.1 parts per million (ppm), while contaminated agricultural land and soils in urban areas have considerably higher concentrations of 1.0 ppm or more. Furthermore, highly industrialized areas have much higher proximate soil levels of cadmium than do areas where little industrial activity occurs. Of considerable concern is the fact that soil cadmium constitutes the single greatest source of cadmium affecting the general population through introduction of the metal into man's food chain via uptake into food crops consumed by humans or livestock.

Data derived from fecal excretion studies and human tissue analyses indicate that most adults (approximately 90 percent) in the United States, on the average, presently ingest less than 25 μg of cadmium in their daily diets. Based on six percent absorption in the absence of nutritional deficiencies, this would correspond to an absorbed value of less than 1.5 μg per person per day from food. Also based on such studies, only about 1 percent of the adult population appears to exceed 50 μg/day dietary cadmium intake, resulting in approximately 3.0 μg retention per day.

It should be pointed out that these values currently apply to existing food levels of cadmium. It is possible that the cadmium content of foodstuffs will increase in the future as a result of use of superphosphate fertilizers. Also, it is possible that food levels may increase as a result of future municipal incineration of high cadmium content sewage sludge or the use of such sludge as agricultural land dressing. In regard to the latter, for example, sludge used for landspreading on agricultural land has been reported to be at times very high in cadmium, ranging up to 1,000 to 3,000 ppm (EPA Multimedia Levels Cadmium, 1977). Thus, given the long residence time of cadmium in soil, without implementation of proper regulatory controls on sewage sludge disposal, dietary cadmium intake would likely rise significantly. However, guidance currently available from EPA, USDA and state agricultural agencies as well as regulatory controls being developed by the EPA under the Clean Water Act and the Resource Conservation and Recovery Act to directly control land application of wastes such as sewage sludge, may help to minimize any future increase in dietary cadmium levels as a result of applying these wastes to agricultural land.

Increased future use of cadmium-containing fossil fuels, as in the combustion of coal, could also be a potential source of increased future dietary cadmium levels, if secondary deposition from the air of cadmium onto agricultural soils were to markedly increase as the result of inadequate emission controls. Increased coal usage, however, is expected to be offset by expanded emission controls.

In addition to ingestion of dietary cadmium as the main route of exposure of most Americans, cigarette smoking has been conclusively shown to add greatly to body burdens of cadmium; and heavy smokers may assimilate as much or more cadmium from cigarettes as they do from the diet. Amounts of respiratory intake from cigarettes range from 4 to 6 μg from two packs smoked per day. This demonstrated added intake of cadmium from cigarettes accounts well for higher levels of cadmium consistently found in urine and kidney tissue of smokers by epidemiologic studies.

1.4.3 Human Population Responses to Cadmium in Human Risk Assessment

1.4.3.1 Summary of human health effects of cadmium--As indicated above, human populations are exposed to cadmium via inhalation and ingestion, and the health effects associated with these routes of exposure are generally chronic in nature.

Of most relevance to human populations are chronic respiratory and renal effects of cadmium. Of these two effects, it is more appropriate to consider chronic renal effects, so the kidney (kidney cortex) is considered the critical organ in chronic exposure to cadmium so far as a public risk assessment discussion is concerned.

Tubular proteinuria is the earliest demonstrable marker for renal dysfunction induced by cadmium, with other effects such as aminoaciduria and glycosuria seen with continued exposure. Renal dysfunction, once manifested clinically in terms of such effects, is often irreversible, as demonstrated by studies on cadmium workers who continued to show renal tubular dysfunction long after cadmium exposure had ceased. Also, cadmium-induced tubular proteinuria is generally accepted as a significant adverse health effect because by the time such an effect is manifested the kidney is already well on the way to increasingly more severe damage and has essentially no reserve for protection against other pathological stresses. This vulnerability is suggested by observations of increased health complications among certain cadmium workers subsequent to their first exhibiting renal tubular proteinurea. In addition, recently reported epidemiology data suggests that significantly increased mortality due to renal disease is experienced by workers occupationally exposed to cadmium.

According to both clinical-epidemiological and model-calculation data, a kidney cortex level of 200 μg Cd/g kidney (wet weight) can be taken as the critical concentration, i.e., the level of cadmium in the kidney (critical organ) at which the earliest discernible adverse effect (the critical effect of renal tubular dysfunction) can be expected to occur.

1.4.3.2 Dose-effect/dose-response relationships of cadmium--As reviewed in the health effects section of this document, the severity of any given marker effect increases as the level of cadmium exposure increases, and the quantitative aspects of response, i.e., the frequency of occurrence of a stated effect in an organism population, comprises the dose-response relationship.

With cadmium, the usual indicators cannot be used to assess the status of the critical organ, the kidney cortex, in terms of that organ's direct exposure to the insulting agent, because measurements of blood or urine cadmium are not precise ways to assess the extent to which the kidney is on its way to functional impairment. Urine cadmium is presently regarded as a better indicator of body burden than blood cadmium. Another strategy has been to define an approximate critical concentration in the kidney cortex above which renal tubular dysfunction can be expected to occur. As was stated earlier, this value is now generally accepted to be 200 μg Cd/g wet weight renal cortex. Using this approach, the probable level of total exposure necessary to produce the critical concentration via ingestion and/or inhalation can then be calculated.

As indicated in the risk assessment chapter of this document, one may use this approach with two previously calculated half-times of cadmium in the body: 18 and 38 years (see Table 1-1). Furthermore, in that chapter (4), the

Table 1-1. CADMIUM EXPOSURE REQUIRED FOR REACHING A KIDNEY CORTEX CONCENTRATION OF 200 μg Cd/g USING DIFFERENT ALTERNATIVES FOR BIOLOGICAL HALF-TIME IN KIDNEY CORTEX AND EXPOSURE TIME[a]

		Levels of cadmium retention or exposure yielding renal dysfunction, assuming cadmium half-times of:	
Basis of calculation[b]	Exposure time (yr)	38 yr	18 yr
		Daily retention (μg)	
Constant daily retention during whole exposure time	10	36	39
	25	16	20
	50	10	13
		Industrial air concentration (in μg/m^3) yielding renal dysfunction	
25% pulmonary absorption, 10 m^3 inhaled per work day, 225 work days/year	10	23	25
	25	11	13
		Daily cadmium intake (μg)	
Food exposure for 50-yr-old person (2500 ca/day) (4.5% retention) (changing caloric intake by age accounted for)	50	250	360
		Corresponding average Cd concentration in foodstuffs (μg/g)	
Total amount (net weight) of food/day 300 g	50	0.8	1.2
600 g		0.4	0.6
1000 g		0.25	0.35

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[a] Adapted from Friberg, L. M. Piscator, G. G. Nordberg, and T. Kjellström. Cadmium in the Environment. CRC Press, Cleveland, 1974.

[b] Assumptions: one-third of whole body retention reached kidney and kidney cortex concentration 50% higher than average kidney concentration. From Nordberg, G. F. (ed.). Effects and Dose-Response Relationships of Heavy Metals. Elsevier, Amsterdam, 1976.

daily retention values of cadmium in the body for these half-times and various exposure periods are determined.

For populations at large, the main factor determining the level of daily cadmium retention is daily dietary intake. This is certainly the case with non-smokers; heavy smoking on the other hand, can lead to retention of amounts of cadmium which approach or even exceed that retained from the dietary intake (see Table 1-2).

Calculations, based on metabolic models, regarding levels of daily dietary intake of cadmium necessary to achieve the critical renal cortex concentration of 200 μg/g associated with renal dysfunction, have yielded widely varying estimates for critical dietary intake levels. Thus, dietary intake levels ranging from 200 to 480 μg/day have been projected as being sufficient to eventually induce proteinuria in the 40- to 50-year-old age group. Various epidemiologic studies have yielded empirical data that fit well with various estimates within the above range of theoretical estimates; a Working Group of Experts for the Committee of European Communities (CEC), however, has tentatively concluded that 200 to 248 μg/day is the best estimate of daily dietary intake necessary to reach the renal critical concentration of 200 μg/g in kidney cortex over a 50 year exposure period for nonsmokers. For smokers, a level of dietary intake of 169 μg/day was estimated as being sufficient for the critical renal cortex concentration to be reached.

The above approaches are aimed at estimating "threshold" dietary intake values necessary to produce a critical cadmium concentration in renal cortex associated with the critical effect of renal tubular dysfunction. Such approaches, however, may not adequately take into account individual biological variability in terms of dietary levels yielding significant renal dysfunction; this is suggested by certain recently published studies on dose-response

Table 1-2. MEDIA CONTRIBUTIONS TO NORMAL RETENTION OF CADMIUM[a]

Medium	Adult	Exposure level	Daily retention (μg)
Ambient air	x20 m^3/d	0.03 μg/m^3	0.15[b]
Water	x2 l/d	3 μg/l	0.36[c]
Food	x2 kg/d	50 μg/day	3.0[d]
Cigarettes packs/day		μg/day[b]	
1/2		1.1	0.70[e]
1		2.2	1.41[e]
2		4.4	2.82[e]
3		6.6	4.22[e]

[a] Modified from: Deane, L. G., D. A. Lynn, and N. F. Surprenant. Cadmium: Control Strategy Analysis. ECA Cong., Bedford, Mass. U.S. Environmental Protection Agency. 1976.

[b] Based on 25 percent deposition and assuming 100 percent absorption of deposited amount.

[c] Based on average American drinking water levels of 3 ppb and assuming 6 percent absorption from gastrointestinal tract.

[d] Based on 6 percent absorption from gastrointestinal tract.

[e] Based on 0.11 μg Cd per cigarette and 6.4 percent retention rate demonstrated by Lewis, G. P., W. J. Jusko, L. L. Coughlin, and S. Hartz. Cadmium accumulation in man. Influence of smoking, alcoholic habit and disease. J. Chron Dis. 25:712-726, 1972.

relationships that relate dietary cadmium intake levels to numbers of individuals in study populations showing increased proteinuria over background levels.

In regard to such dose-response aspects of cadmium exposure, i.e., defining that proportion of a target population that would be expected to show a given health effect at a particular level of cadmium exposure, there exist both modeling and empirical data (see Chapter 4) which have been recently compiled into a dose-response framework. Using renal tubular dysfunction as the adverse health effect for which response rates were calculated and daily dietary intake of cadmium as the exposure variable, the theoretical framework predicts increasing response rates for renal damage as a function of dietary intake of cadmium. According to that theoretical framework, a daily dietary intake of 60 μg/day, for example, would be predicted to produce, by age 50, a renal dysfunction response rate of 1.0 percent of this age-group population. Further, at daily cadmium intake rates of 80 and 100 μg/day, approximately 2.5 percent and 5 percent of the population, respectively, would be predicted to sustain renal tubular injury. Actual, observed prevalence rates in certain epidemiologic studies appear to fall in the general range of predicted rates for dietary levels markedly above 100 μg/day. However, due to the lack of much empirical data for lower dietary intake levels, little confidence can now be placed in the rates predicted for dietary levels under 100 μg/day. Also, certain other reservations concerning key assumptions underlying the model, as discussed in Chapter 4, argue against employing its predictions for risk assessment purposes at the present time.

In regard to empirical dose-response data relating dietary cadmium intake levels to prevalence of renal dysfunction, evidence has been reported for statistically significant increases in cadmium-induced proteinuria occurring in Japanese over 50 years of age as the result of chronic dietary cadmium intake of approximately 100-150 μg/day. An equivalent intake level of 150-200 μg/day would obtain for Europeans/Americans, taking into account larger body and kidney sizes of the latter in comparison to the Japanese.

1.4.3.3 Populations at risk to the adverse health effects of cadmium--Populations at risk are those segments of a defined population exhibiting characteristics associated with a significantly higher probability of developing an abnormal condition, illness, or status. This enhanced risk may come about because of some greater inherent susceptibility or from exposure situations peculiar to that group.

In the case of cadmium, based on the collective experience with widespread exposure in Japan and other data cited in this document, certain large segments of the United States population can be identified as potentially being at risk for experiencing adverse health effects associated with exposure to the metal. Generally speaking, other than for certain occupationally exposed workers, acute toxic effects of cadmium are not of much concern in assessing its potential public health impact in the United States. Rather, chronic effects, mainly renal dysfunction or damage, are of primary concern due to the propensity of cadmium to accumulate in the body (especially in the kidney) over very long time periods, e.g., for 40 to 50 years or more.

Given the fact cadmium is retained in the kidney over long time periods, then it is not surprising that older segments of various populations studied (i.e., those over 45 to 50 years of age) have generally been found to have the highest levels of cadmium in the kidney and also to display the highest incidence of renal dysfunction. Based on this, it would appear that those individuals in the United States population over 40 to 50 years old are most immediately at risk for exhibiting cadmium-induced renal dysfunction as a consequence of further cadmium exposure. Also, given the dependence of cadmium absorption on nutritional factors, e.g., increased uptake in the presence of iron, zinc, or calcium defiency, the risk would be greatest among those Americans who are poorly nourished.

It is obviously the case that aging affects all members of any population and, in view of that, the entire population of the United States must therefore be viewed as being at potential risk for adverse effects associated with cadmium exposure. In fact, due to the accumulation of cadmium in the kidney essentially over an entire lifetime, present cadmium exposure levels and any future increments in exposure, in the long run, would be expected to impact most heavily on present younger members of the population. Thus, any assessment for the American public of potential risk associated with cadmium exposure must attempt to project the likely eventual consequences of present and/or increased cadmium exposure levels for the general United States population. In attempting to make such projections, dietary cadmium intake, as the chief source of cadmium for the general public, is of primary concern in the analysis.

In regard to current daily dietary cadmium intake levels for Americans, different estimates have been generated depending upon the measurement approaches employed. FDA "market basket" surveys, for example, have yielded estimates ranging from approximately 30 to 50 μg/day, or up to approximately 70 μg/day for teenage males. On the other hand, more recent estimates based on fecal cadmium excretion measurements tend to be much lower, i.e., with mean dietary intake for adult non-smokers being around 18 μg/day and approximately 90 and 99 percent of the population being below 25 and 50 μg/day, respectively.

It is next necessary to compare the above estimate(s) of current daily dietary cadmium intake with ingestion levels that, over an extended period of time (40 to 50 years), will lead to sufficient cadmium being accumulated in the kidney so as to induce the critical effect associated with chronic cadmium exposure, i.e., renal tubular dysfunction. As noted earlier in the present summary and discussed in more detail in Chapter 4 of this document, various modeling approaches have yielded estimates ranging from 200 to 480 μg/day as the requisite ingestion level eventually resulting in the critical renal cortex cadmium concentration of 200 μg/g wet weight being reached and, thus, associated renal dysfunction occurring. Also as noted earlier, a concensus of opinion among a group of experts working for the Committee of European Communities (CEC) was that 200 to 248 μg/day is probably the best estimate of the critical daily cadmium ingestion level necessary to induce renal dysfunction. If the latter view is accepted, then American dietary cadmium intake levels of 10 to 50 μg/day would be from approximately 4 to 25 fold less than ingestion levels estimated to yield renal dysfunction over a 50 year exposure period. For some individuals with distinctly higher than average dietary cadmium intake levels, (less than 1 percent exceeding 50 μg/day), that margin would be less. Also, certain other population groups can be identified as potentially being at special risk.

More specifically, based on data discussed previously, cigarette smokers constitute a large population at special risk for cadmium-induced renal effects. In regard to increased risk for smokers, tabulations have been carried out in an effort to demonstrate the relative contribution of cigarette smoking to the total daily added burden of cadmium (daily retained cadmium) as a function of the amount of cigarettes consumed (see Table 1-3). For example, assuming a 25 μg/day daily dietary intake level, smoking one, two, or three packs of cigarettes daily can contribute as much or more than the average level of cadmium retained due to dietary ingestion, as illustrated in the table. When the amounts of cadmium retained daily in individuals who smoke heavily are compared to critical daily retention values (10 to 13 μg/day) above which the critical concentration of cadmium in kidney will eventually be exceeded, the relative margin of safety for exposure to other sources of cadmium is significantly reduced. Thus, at present, cigarette smokers who constitute a large portion of the United States population are at greater risk for cadmium-induced renal dysfunction than non-smokers.

Another group at possible risk for adverse health effects of cadmium are those with unusual dietary habits, such as vegetarians and those consuming large quantities of shellfish (e.g., oysters) over an extended period of time. These groups might also become at greater future risk in the event that cadmium levels in their preferred foodstuffs were to substantially increase in the future.

Based on studies demonstrating children to be a special risk group for exposure to other heavy metals (e.g., lead), one might analogously hypothesize that children may be another population segment at potential risk for increased exposure to cadmium. Such increased risk, however, is questionable in terms of projected lifetime tissue accumulations of cadmium except in cases where unique behavior patterns of children, e.g., mouthing of non-food objects, would bring them into contact with quite high levels of cadmium-contaminated house dust or soils. Unfortunately, very little empirical data is presently available by which to ascertain to what extent such exposures may occur; but such occurrences are likely relatively rare.

Table 1-3. ESTIMATED RELATIVE CONTRIBUTION OF DIETARY INTAKE, CIGARETTE SMOKING AND AMBIENT AIR CADMIUM LEVELS TO TOTAL DAILY CADMIUM RETENTION FROM ALL SOURCES[a]

Dietary Intake (Net Retention)	Smoking Status (Net Retention)	Air Cadmium Levels (Net Retention)				
		0.0 ng/m^3 (0.0 µg/day)	1.0 ng/m^3 (.005 µg/day)	10 ng/m^3 (.05 µg/day)	100 ng/m^3 (.50 µg/day)	1000 ng/m^3 (5.0 µg/day)
Food Level A = 25 µg/day (1.50 µg/day)	Non-smoker (0.00 µg/day)	1.86 (0;0%)*	1.87 (0;0%)*	1.91 (0;3%)	2.36 (0;21%)	6.86 (0;73%)
	½ pack/day (0.70 µg/day)	2.56 (27;0%)	2.57 (27;0%)	2.61 (27;2%)	3.06 (25;16%)	7.56 (10;66%)
	1 pack/day (1.41 µg/day)	3.27 (43;0%)	3.28 (43;0%)	3.32 (42;2%)	3.77 (40;13%)	8.27 (17;60%)
	2 pack/day (2.82 µg/day)	4.68 (60;0%)	4.69 (60;0%)	4.73 (60;1%)	5.18 (57;10%)	9.68 (29;52%)
	3 pack/day (4.22 µg/day)	6.08 (69;0%)	6.09 (69;0%)	6.13 (69;1%)	6.58 (67;8%)	11.08 (38;45%)
Food Level B = 50 µg/day (3.00 µg/day)	Non-smoker (0.00 µg/day)	3.36 (0;0%)	3.37 (0;0%)	3.41 (0;1%)	3.86 (0;13%)	8.36 (0;60%)
	½ pack/day (0.70 µg/day)	4.06 (17;0%)	4.07 (17;0%)	4.11 (17;1%)	4.56 (15;11%)	9.06 (8;55%)
	1 pack/day (1.41 µg/day)	4.77 (30;0%)	4.78 (30;0%)	4.82 (29;1%)	5.27 (27;9%)	9.77 (14;51%)
	2 pack/day (2.82 µg/day)	6.18 (46;0%)	6.19 (46;0%)	6.23 (45;1%)	6.68 (42;7%)	11.18 (25;45%)
	3 pack/day (4.22 µg/day)	7.58 (56;0%)	7.59 (56;0%)	7.63 (55;1%)	8.08 (52;6%)	12.58 (34;40%)
Food Level C = 75 µg/day (4.50 µg/day)	Non-smoker (0.00 µg/day)	4.86 (0;0%)	4.87 (0.0%)	4.91 (0;1%)	5.36 (0;10%)	9.86 (0;51%)
	½ pack/day (0.70 µg/day)	5.56 (13;0%)	5.57 (13;0%)	5.61 (12;1%)	6.06 (12;9%)	10.56 (7;47%)
	1 pack/day (1.41 µg/day)	6.27 (23;0%)	6.28 (23;0%)	6.32 (22;1%)	6.77 (21;7%)	11.27 (13;44%)
	2 pack/day (2.82 µg/day)	7.68 (37;0%)	7.69 (37;0%)	7.73 (36;1%)	8.18 (34;6%)	12.68 (22;39%)
	3 pack/day (4.22 µg/day)	9.08 (45;0%)	9.09 (46;0%)	9.13 (46;1%)	9.58 (44;5%)	14.08 (30;36%)

*Each first value equals total daily cadmium retention levels (in µg/day) from all sources, assuming constant daily retention from water of 0.36 µg/day derived from consumption of water with average cadmium concentration of 3 ppb. The two values in parentheses ( ) indicate percentage of total daily cadmium retention attributed to cigarette smoking and ambient air cadmium exposure, respectively, at a given ambient air cadmium level.

[a] Note that daily cadmium retention of 10 µg/day would be projected to result in a critical cadmium concentration of 200 µg/g wet weight of kidney cortex being reached over a 50-year exposure period, assuming a kidney half-time for cadmium of 38 years. A comparable retention value of 13 µg/day would obtain if a kidney half-time for cadmium of 18 years is assumed.

1.4.4 Overall Conclusions

Uptake of cadmium in man via a variety of routes of exposure can result in serious adverse health effects. These include significant irreversible pulmonary and renal damage that typically occur as a result of chronic occupational and non-occupational exposure.

The levels of chronic cadmium exposure necessary to induce significant renal dysfunction, the "critical effect" typically observed earliest with ambient environmental exposures, may not exceed by much the levels presently encountered by some Americans via dietary intake and other exposure media, especially cigarette smoking. Thus, uncontrolled increases in cadmium exposure from whatever source may reduce an already low margin of safety before adverse effects would be expected to occur in some members (especially smokers) of the American population.

As for ambient air as a possible source of increased environmental cadmium exposure, calculations summarized in Table 1-3 suggest that, in general, ambient air exposures below 10 ng/m^3 do not significantly increase kidney cortex concentrations of cadmium, whereas at 100 ng/m^3, notable accumulations of renal cadmium begin to occur and, by 1000 ng/m^3, approach critical exposure levels for induction of renal dysfunction (in conjunction with background dietary exposures). As discussed in Chapter 4 under Exposure Sources, annual average ambient air levels of cadmium in the vicinity of certain cadmium-emitting industrial facilities or municipal incinerators have been estimated to exceed 100 ng/m^3, but few appear to approach 1000 ng/m^3. Table 1-4 presents estimates of the numbers of Americans exposed to various annual average concentrations of cadmium in air derived from different current major emission sources.

TABLE 1-4. AVERAGE EXPOSURE AND NUMBER OF PEOPLE EXPOSED TO ANNUAL AIR CADMIUM LEVELS GREATER THAN 0.1 ng/m^3 BY SPECIFIED SOURCE TYPES[a]

	AVERAGE EXPOSURE		MAXIMUM EXPOSURE	
	Concentration (Annual Avg. ng/m^3)	Population (10^3 People)	Concentration (Annual Avg. ng/m^3)	Population (10^3 People)
Source				
Secondary Smelters				
Copper	1.51	9,891	>10	296
Zinc	0.5	37	0.1-1	37
Municipal Incinerators	8.4	48,270	>100	1.0
Primary Smelters				
Zinc[b]	86-110	376	>1,000	0.1-0.8
Lead[b]	9-11	105	100-1,000	0-0.2
Copper[b]	5.2-8.0	218-352	100-1,000	0-0.2
Cadmium[b]	3.0-15.0	150	>1,000	0-2.6
Iron and Steel	2	19,896	>10	372

[a] From EPA Assessment of Human Exposure to Cadmium (1979).

[b] Ranges result from differing assumptions concerning fugitive emissions; see text, Section 6.

Several recent developments in waste management, energy production, and food production appear to have the potential for markedly changing the present United States population exposure profile for cadmium. Specifically, substantially increased ambient air levels of cadmium could result from future expanded municipal incineration of solid waste materials and expanded fossil fuel use, especially increased coal combustion, if emissions from these sources are not adequately controlled. Also, future uncontrolled expanded agricultural use of cadmium-contaminated phosphate fertilizers or high-cadmium content sewage sludge could potentially introduce increased amounts of cadmium into the human food chain and thereby raise levels of dietary cadmium. In view of the above, regulatory action addressing any single source of exposure, but not taking into account all other possible sources of exposure and expected changes in levels resulting from them, may not be adequate in terms of truly safeguarding the public health. Instead, a well-coordinated comprehensive plan for controlling exposure of the general population would be desirable.

2. BIOLOGICAL SIGNIFICANCE AND ADVERSE HEALTH EFFECTS OF CADMIUM

2.1 INTRODUCTION

A variety of biological and adverse health effects have been documented in both man and experimental animals under conditions of acute and chronic exposure to cadmium. These responses are discussed in this section.

From the standpoint of relevance of these effects to the hazards posed by cadmium on populations at large, the chronic effects are considerably more important than those of an acute nature. In turn, those chronic effects elicited by ingestion of the element are probably of more significance than that by inhalation, although this should not be taken to mean that the opposite might not be the case in certain situations. Studies involving the parenteral administration of the metal to experimental animals are also included because they are potentially valuable in defining the metabolic and toxic parameters of cadmium.

Assessment of the effects of an element follows closely on an understanding of the element's metabolism in an organism. Therefore, the first section of this report deals with the absorption, transport, distribution, and excretion of cadmium in man and animals.

Systemic effects of cadmium are, in large measure, macroscopic manifestations of injury at the cellular, subcellular, and molecular level. Thus, enzymological, subcellular and cellular studies, both *in vivo* and *in vitro*, are discussed first along with consideration of the role of metallothionein. Studies of the effects of cadmium on various specific organ systems are reviewed and evaluated next. Special attention is accorded the renal, pulmonary, cardiovascular, and reproductive systems.

Also discussed are endocrine, skeletal, hepatic, gastrointestinal, neural, and immunosuppressive effects of the metal.

No toxic element functions in a metabolically static milieu, and this is especially true of cadmium. Therefore, discussion of the effects of cadmium should take into account various interactions between cadmium and other elements which either ameliorate or potentiate its effects. This includes, for example, cadmium/zinc, cadmium/selenium, cadmium/calcium, and cadmium/iron relationships. The interactive effects of these metal/metal combinations are discussed in a separate, final section in addition to being alluded to in other sections where appropriate.

2.2 METABOLISM OF CADMIUM

No discussion of the health effects of a toxic substance is complete without consideration of the metabolism of that element, i.e., the processes of absorption, transport, deposition, remobilization in organs, and excretion.

While a sizable body of data exists on the quantitative and qualitative aspects of cadmium metabolism in man and experimental animals, the present report is concerned with those features of cadmium metabolism that impinge directly on health effects and is not meant to be an exhaustive review of the relevant literature.

2.2.1 Sources of Exposure

Cadmium, like other multimedia environmental contaminants such as lead, is introduced into the host organism from several sources including air, food, and water. Information on amounts of cadmium encountered in various media is considered later in a separate section on exposure in the risk-assessment portion of the present report.

2.2.2 Inhalation

Factors that require consideration in dealing with pulmonary absorption include the physiochemical features of the form of airborne cadmium at the time of external exposure, as well as subsequent handling of the deposited form of cadmium in the respiratory tract. The extent of deposition in the various pulmonary tract compartments is a function of particle size and solubility. The quantitative features of this relationship have been reviewed by the Task Group on Lung Dynamics (1966), Fulkerson and Goeller (1973), Friberg et al. (1974), and Nordberg (1974). Cadmium-containing matter (usually aerosols) in air is lodged in the lungs and the tracheobronchial tract in quantities inversely related to particle size; lung deposition is about 50 percent for particles of 0.1 micrometer mean mass diameter (MMD) ranging down to 10 percent for particles with MMD of 5 micrometers.

Part of the inhaled material deposited in the respiratory tract undergoes retropassage via ciliary activity and is then swallowed. Factors governing this portion of the intake are therefore related to gastrointestinal absorption, which is discussed below. Many of the earlier studies on retention time of inhaled cadmium in the form of aerosols or fumes are not amenable to interpretation due to lack of knowledge about particle size. The Task Group on Lung Dynamics (1966), however, has arrived at a half-time range of several days to a year for retention of cadmium in the lung. Systemic absorption from the lung of inhaled cadmium is estimated for man to range from less than 20 to 50 percent, depending on particle size, solubility of the cadmium compound, etc. Animal studies provide figures of 10 to 40 percent (Friberg et al., 1974; Elinder et al., 1976; WHO, in press).

2.2.3 Gastrointestinal Absorption

Human populations generally acquire the major part of their cadmium intake from the diet and some from water. The amount of such intake is discussed elsewhere in this report. The extent of gastrointestinal absorption of ingested cadmium in man is about six percent; it is somewhat less in animals (Friberg et al., 1974; Nordberg, 1976). Dietary factors, as well as the chemical form of the metal, play a role in modifying this figure, with certain nutritional deficiencies leading to an enhancement of cadmium absorption in man and animals (Friberg et al., 1974). As a specific example, the group most affected with the symptomatology of Itai-Itai disease in Japan were women who had a history of Vitamin D and calcium deficiency (see Health Effects and Epidemiology sections).

2.2.4 Other Absorption Routes

Two other routes of absorption may potentially play a role in the exposure of humans to cadmium: cutaneous absorption and transplacental transfer. Cutaneous cadmium absorption has been shown in animals (Skog and Wahlberg, 1964; Wahlberg, 1965; Kimura and Otaki, 1972); however, this route is probably minor in man compared to inhalation and ingestion. Transplacental transfer is discussed in the Reproduction and Development section (2.7) of this chapter.

2.2.5 Transport and Deposition

Blood is the vehicle for transport of cadmium via inhalation or ingestion and the kinetics of its movement in the body rest heavily on the type of exposure (Friberg et al., 1974). What constitutes "normal" blood levels of cadmium is a subject of controversy as is discussed later in the Risk Assessment section (4.).

Animal studies (Friberg et al., 1974) show that, in the time immediately following parenteral administration of cadmium ion, most of blood cadmium is found in plasma. Furthermore, there is initially a rather rapid clearance of cadmium from blood. This is followed by a slower decline and a subsequent rise in in the Cd content of both plasma and cells, with a larger comparative amount accumulating in the erythrocyte. This increase corresponds to the time required for enhanced metallothionein synthesis. The half-time of blood cadmium following cessation of a chronic exposure appears to be about six months (Friberg et al., 1974).

Much data exist on the relative distribution of cadmium among various organs in man and experimental animals and these have been reviewed (Friberg et al., 1974; Nordberg, 1972). In populations with minimal exposure to cadmium, about half of the organ distribution of cadmium is in liver and kidney, with kidney accounting for 30 percent of the total body burden. A higher proportion of cadmium is found in liver during chronic exposure because of cadmium-induced synthesis of metallothionein in the liver. Other organs that accumulate cadmium include the testes, lungs, pancreas, spleen, and various endocrine organs. In contrast, relatively low concentrations of cadmium are found in bone, brain, and muscle tissue. However, due to the much greater mass of muscle versus liver and kidney tissue, the absolute amount of cadmium found in muscle within a given mammalian organism can be considerable.

Simple model projections for the half-time value for cadmium in various organs predict, for example, a value between 17.6 yr (Tsuchiya and Sugita, 1971) and 38 yr (Kjellstrom, 1971) for kidney and kidney cortex in man. Although these values were derived from data on representative samplings of Japanese and American populations, Nordberg (1976) has cautioned that they involved use of a simple model dependent on a fixed fraction of cadmium directly transferred to kidney, whereas the true picture is rendered more complex by hepatic-renal transfer of cadmium. Nevertheless, the simple model is still useful for most practical purposes.

Metallothionein, it should be noted, plays a major role in the movement and excretion of cadmium *in vivo* in various species. Details concerning this cadmium-binding protein are presented in a subsequent section (section 2.3.2).

2.2.6 Excretion

Excretion of cadmium by man and experimental animals is mainly via the urinary and gastrointestinal tracts. Since only about six percent of cadmium is absorbed from the gastrointestinal tract, the bulk of ingested cadium is lost in feces. Thus, it is difficult to assess the relative differential excretion of absorbed cadmium by the renal and intestinal routes. Renal excretion in the urine, nevertheless, is of a magnitude such that it can be taken as a relatively good indicator of internal exposure. Urinary output is seen to increase slowly with age as the cadmium body burden increases. In the presence of renal dysfunction, however, urinary levels of cadmium may rise markedly. That is, in both animals and man, it has been observed that only relatively small amounts of cadmium are excreted in the urine early in exposure, but sudden increases then occur concomitantly with the appearance of proteinuria or other signs of renal damage (Friberg, 1952; Axelsson and Piscator, 1966; Nordberg and Piscator, 1972; Suzuki, 1974; Friberg *et al*., 1974; Lauwerys *et al*., 1974; Singerman, 1976).

In man, under conditions of low-level, chronic cadmium exposure, cadmium loss via the urine is typically < 1 μg/day (Johnson *et al*., 1977; Elinder *et al*., 1978) for non-smokers. For smokers and other cadmium-exposed individuals, urinary cadmium values are higher; and there appears to be some overall relationship between urinary excretion of cadmium and total body burden. While it has been demonstrated that biliary excretion occurs in animals, it has yet to be demonstrated that it is a significant factor in man (Stowe, 1976; Cherian, 1977; Cherian and Vostal, 1977).

2.3 SUB-CELLULAR AND CELLULAR ASPECTS OF CADMIUM TOXICITY

Various studies focusing on the toxic effects of cadmium at the cellular and sub-cellular level are discussed in this section. Types of effects discussed include: (1) general subcellular effects, e.g., the interaction of cadmium with enzymes and non-enzymic biomolecules crucial to the physiological functioning of the organism and (2) the induction of metallothionein and its role in cadmium metabolism and toxicity.

2.3.1 General Sub-Cellular Effects

The literature on the interaction of cadmium with enzymes spans a spectrum of effects, ranging from the observation of nonspecific activation or inhibition of purified enzyme preparations *in vitro* to enzymic effects that may contribute to a significant part of the *in vivo* pathology of cadmium.

Since much of the former tends to have little relevance to *in vivo* conditions, much of the data is not given detailed consideration here. Rather, one is directed to a more general review, such as that of Vallee and Ulmer (1972). In some cases, it is more appropriate to discuss enzyme effects as part of the systemic toxicity of cadmium; this is done elsewhere in this report.

There are several mechanisms by which cadmium may influence enzyme function. The metal ion may interact with the enzyme directly via the marked affinity of cadmium for the sulfhydryl and imidazolyl nitrogen groups at sites necessary for enzyme function and may even substitute for native metal ions in various metalloenzymes, as in the case of substituting for zinc in zinc metalloenzymes. Similarly, cadmium may interact with the substrate for an enzyme, sufficiently perturbing the conformation to markedly alter enzyme-substrate binding kinetics. Circulating levels of enzymes may also be altered due to organ derangement and cellular release, as in the case of changes in marker enzymes for hepatic function. Another important mechanism, particularly in cases of zinc deficiency, may be alterations in the pattern of distribution of zinc.

Virtually all of the studies dealing with the cellular and sub-cellular aspects of cadmium toxicity have involved experimental animals. In Table 2-1 are tabulated the various effects reported, divided as to whether the studies were *in vivo* or *in vitro* in nature. In the text, *in vivo* and *in vitro* studies are discussed together under the different types of subcellular effects or sites studied. It should be noted that many of the dosages employed are well above what might be encountered by man.

A number of reports indicate that cadmium has an effect on metabolizing enzymes of organisms. For example, Furst and Mogannam (1975) have reported

TABLE 2-1. SUBCELLULAR AND CELLULAR CADMIUM TOXICITY IN EXPERIMENTAL ANIMALS

Species	Cd Dose*	System(s) studied**	Effect(s) found**	Reference
In vivo Studies				
Rat	2.5 or 3.8 mg/kg b.w.; i.p.	Hepatic drug-metabolizing enzymes	25 to 60% inhibition of aniline hydroxylase and nitro reductase activity; 50% reduction of microsomal P-450 content	Teare et al., 1977
Rat	2.0 mg/kg b.w.; single; i.p.	Hepatic drug-metabolizing enzymes	24% increase in hexobarbital sleeping time; 27% reduction in cytochrome P-450; 44% reduction in cytochrome b_5; 57% inhibition of amino pyrine demethylase (3rd day post-injection); 32% aniline hydroxylase inhibition of (3rd day post-injection)	Krasny and Holbrook, 1977
Mouse	5 and 3 mg/kg b.w.; i.p.; after i.p. injection of 3 methyl cholanthrene/ octanoin solution	Hepatic drug-metabolizine enzymes	Total inhibition of AHH activity at higher dose; little inhibition of AHH activity at lower dose	Furst and Mogannam, 1975
Rat	0.25 and 1.0 mg/kg b.w.; i.p. daily for 21 or 45 days	Cyclic AMP and associated enzymes	Increase in cyclic AMP level; increase in both basal and fluoride-stimulated activity	Singhal et al., 1976

TABLE 2-1. SUBCELLULAR AND CELLULAR CADMIUM TOXICITY IN EXPERIMENTAL ANIMALS (CONTINUED)

Species	Cd Dose*	System(s) studied	Effect(s) Found**	Reference
Rat	100 ppm in drinking water; *ad lib.* for *30 days*	Enzymes of duodenal mucosa	Decrease in brush-border ATP-ase activity; decrease in alkaline phosphatase activity; increase in isocitrate dehydrogenase activity; increase in G-6-PD activity	Sugawara and Sugawara, 1975
Rat	3.2 mg/kg (0.03 m mole/kg); single i.p.	Dehydrogenase enzyme activity	89% inhibition of succinic dehydrogenase activity in liver and testis; increase in lactate dehydrogenase activity	Singh and Nath, 1975
Rat	300 ppm in drinking water; ad lib.	Osidatine phosphorylation	Reduction in respiration and P/O ratios; increase in mitochondrial cytochrome A and cytochrome C	Kamata *et al.*, 1976
Rat	0.34 to 3.4 mg/kg b.w.; i.p.	RNA synthesis in hepatic fractions	Inhibition of RNA synthesis in hepatic nuclei; significant inhibition of polyuridylic acid-directed incorporation of L-(^{14}C)-phenylanine in microsomes	Stoll *et al.*, 1976
Rat	2 mg/kg b.w.; once per wk.; for 2 to 3 wk.	Protein synthesis by ribosomes	Inhibition of protein synthesis in isolated ribosomes using an amino-acid incorporating system	Norton and Kench, 1977

Table 2-1. SUBCELLULAR AND CELLULAR CADMIUM TOXICITY IN EXPERIMENTAL ANIMALS (CONTINUED)

Species	Cd Dose*	System(s) studied**	Effect(s) found**	Reference
Rat	--	Cyclic AMP and associated enzymes of tissue homogenates	Inhibition of both cyclic AMP phosphodiesterase and adenylate cyclase activity	Anthanson and Bloom, 1976
Turkey	Up to 0.7 mM	Adenylate Cyclase activity in erythrocyte membrane	Up to 100% inhibition (at 0.7 mM) of both forms of adenylate cyclase activity	Spiegel et al., 1976
Turkey; mouse; rabbit; guinea pig; dog; cat	1 x 10^{-4} M	Renal ATP-ase activity	Inhibition of renal Na+-K+ ATPase 10 times greater than Mg++ ATPase for all species tested	Nechay and Saunders, 1977
Rat	20 ppm in the preparations	Kidney, intestine, and salivary gland (homogenates) phosphatases	13 to 20% inhibition of acid phosphates in all preparations; 40% inhibition of alkaline phosphatase in salivary gland	Iqbal et al., 1976
Chick	2.5 x 10^{-5}M and greater	25-hydroxy-Vitamin D_3 metabolism	Complete inhibition of 1,25-dihydroxy-Vitamine D_3 at lowest level	Suda et al., 1974
Rat	0.5-3.0 μM	Liver mitochondria respiration	Uncoupling of oxidative phosphoratin; acceleration of State IV respiration	Kamata et al., 1976
Rabbit	Up to 3mM in medium for 20 hr.	Alveolar macrophages tissue culture	Reduction of cell viability; reduction of phophatase activity; disturbance in morphology (Cd 1 of 2 most toxic metals studied)	Waters and Gardner, 1975

Table 2-1. SUBCELLULAR AND CELLULAR CADMIUM
TOXICITY IN EXPERIMENTAL ANIMALS (CONTINUED)

Species	Cd Dose*	System(s) studied**	Effect(s) found**	Reference
Mouse	4.3 mg/kg b.w. (LD_{50}) i.p.	Heterolysosome formation and function in kidney and liver	Inhibition (increasing over time) of proteolysis in liver particles 2 to 20 hr. after injection; less effect on kidney particles	Mego and Cain, 1975
Mouse	0.15 mg/kg b.w.; intragastric dose for 90 days	Catalase and carbonic anhydrase activity	Decrease in carbonic anhydrase activity in liver, kidney, and blood after 20 days; decrease in catalase activity after 60 days	Ogawa *et al.*, 1973
Mouse	50 ppm in drinking water for up to 8 mo.	Subcellular localization of Cd	Localization of Cd mainly in apical vessicles, lysosomes, lysosomes, and proximal tubular cells	Popham and Webster, 1976
Rat	2.1 mg/kg b.w.; single injection with ^{115}Cd tracer	Liver localization of Cd	Appearance of label in nucleus and cytoplasmic fractions; concentration of nuclear Cd higher in non-hostine protein	Hidalgo and Bryan, 1977
Rat	2 mg/kg/wk for 2 to 3 wk. by injection	Subcellular localization of Cd	Appearance of significant amounts in purified ribosomes and enzyme preparations	Norton and Kench, 1977
In Vitro Studies				
Rat	Various concentrations of Cd and other heavy metals	AHH of 10% liver homogenate	Marked inhibition of AHH complex with Cd most inhibitory of all ions studied	Tsang and Furst, 1976

Table 2-1. SUBCELLULAR AND CELLULAR CADMIUM
TOXICITY IN EXPERIMENTAL ANIMALS (CONTINUED)

Species	Cd Dose*	System(s) studied**	Effect(s) found**	Reference
Mouse	About 4 mg/ml medium and higher	Alveolar macrophages, peritoneal macrophages, and polymorphonuclear neutrophils	Significant depression of respiratory burst when heat-killed *P. aeruginosa* added to medium	Loose *et al.*, 1977
Hamster	2.2×10^{-5} M	Phagocytic activity of alveolar macrophages	Significant reduction in phagocytic index (PI)	Graham *et al.*, 1975
C^3H-strain mouse	15.6 mg/ml medium	L-strain fibroblasts	Disappearance of ribosomes; changes in mitochondria including total destruction; swelling of endoplasmic reticulum	Kawahara *et al.*, 1975
Mouse	2.8 to 88.0 mM (0.3 to 9.4 mg/ml)	Subcutaneous connective-tissue L-cells	Reduction in cell viability; cellular LD_{50} 5.5 for exponential phase, 30.5 for stationary phase	Ozawa *et al.*, 1976

*Abbreviations: b.w.: body weight; i.p.: intraperitoneal injection; ppm: parts per million; --: information not available

**Abbreviations: AHH: aryl hydrocarbon hydroxylase; G-6-PD: glucose-6-phosphate dehydrogenase
Cyclic AMP: adenosine 3':5'-cyclic phosphate

that inhibition of the inducible enzyme complex aryl hydrocarbon hydroxylase (AHH) occurs in mice given 3-methylcholanthrene intraperitoneally (i.p.) in trioctanoin (0.01 ml/g) and cadmium ion in one of two injected doses: 5 mg/kg and 3 mg/kg. At the higher dose, enzymic activity was almost completely quenched, while little inhibition was noted at the lower exposure level. In a related in vitro study, using a 10 percent liver homogenate, Tsang and Furst (1976) showed marked inhibition of this enzyme complex by five different metal ions, of which cadmium was the most inhibitory.

An acute effect of cadmium on hepatic metabolizing enzymes in the rat was noted by Teare et al. (1977). A single i.p. injection of cadmium chloride at levels of either 2.5 or 3.8 mg/kg into male rats produced significant (25 to 60 percent) inhibition of aniline hydroxylase and nitroreductase activity and reduced microsomal P-450 content to about 50 percent of control values. These effects are not seen with o-demethylase activity. Complicating these observations is an apparent "buffer effect", the last-named enzyme showing inhibition in phosphate buffer and more significant inhibition in Tris buffer.

Krasny and Holbrook (1977) assessed various parameters of drug metabolism in rats following a single i.p. dose of cadmium acetate (2.0 mg/kg). At 3 days post-exposure, hexobarbital-induced sleeping time was increased 24 percent while microsomal levels of cytochromes P-450 and b_5 were decreased by 44 percent and 27 percent, respectively. At day 7 these values returned to normal. The microsomal enzymes aminopyrine demethylase and aniline hydroxylase both showed inhibition: the former, 47 and 37 percent at days 3 and 7, and the latter, 32 and 23 percent at these same time points. Heme oxygenase showed the greatest increase (350 percent of control) at 2 days post-injection, returning to normal at the end of 1 wk, while biliverdin reductase activity was not altered at any time.

Several reports have appeared describing the in vivo and in vitro effects of cadmium on adenylate cyclase and other components of cyclic AMP (adenosine 3':5'-cyclic phosphate) metabolism in animals.

Singhal et al. (1976) observed that, while chronic cadmium treatments in rats (daily i.p. injection of 0.25 or 1.0 mg/kg for 21 or 45 days) failed to alter AMP-phosphodiesterase activity, the amount of cyclic AMP and the activity of basal and fluoride-stimulated forms of hepatic adenylate cyclase were markedly increased. However, the amount of cyclic AMP binding to hepatic protein kinase was decreased, as was the kinase activity ratio.

In an in vitro study, Nathanson and Bloom (1976) have shown that both basal and hormone-stimulated adenylate cyclase activity of various tissue homogenates and their particulate fractions were inhibited by very low levels of cadmium and other heavy metal ions. Cadmium also inhibited cyclic AMP phosphodiesterase activity.

Using turkey erythrocyte membranes, Spiegal et al. (1976) showed cadmium inhibition of all forms of adenylate cyclase activity, with 100-percent inhibition at 0.7 millimolar (mM) concentration (78 μg/ml). Such effect could be offset by the use of mercaptoethanol and British anti-Lewisite (BAL), both metal chelants.

Nechay and Saunders (1977) studied the effects of cadmium on renal adenosinetriphosphatase (ATPase) preparations from various regions of kidney obtained from dog, cat, rat, rabbit, guinea pig, and mouse. At cadmium levels of 10^{-4} M, Na^+-K^+ ATPase was inhibited, regardless of source or type of enzyme preparation, with the effect being ten-fold greater than the corresponding inhibition of Mg^{++}-ATPase. The inhibitory effects were not altered by sodium or potassium levels, but were decreased by ethylenediaminetetraacetic acid (EDTA) addition.

Sugawara and Sugawara (1975) studied the effects of cadmium administration (100 ppm cadmium solution _ad libitum_ for 30 days) on selected enzyme activity in duodenal mucosa in male Wistar rats. Inhibition of brush border ATPase and alkaline phosphatase and increase in the activities of isocitrate dehydrogenase and glucose-6-phosphate dehydrogenase (G-6-PD) were noted. Such _in vivo_ effects could not be duplicated, however, with _in vitro_ studies using comparable cadmium levels.

Iqbal _et al_. (1976) studied the _in vitro_ effect of cadmium on phosphatases using homogenates of kidney, intestine, and salivary gland. Cadmium at 20 parts per million (ppm) inhibited acid phosphatases 13 to 20 percent in all these preparations, while significant inhibition of alkaline phosphatases (40 percent) at this level was seen only in a salivary gland preparations. Prior addition of zinc ion abolished the inhibitory effect of cadmium on alkaline phosphatase but had little effect on acid phosphatase.

Both _in vitro_ and _in vivo_ inhibition of succinic dehydrogenase and lactate dehydrogenase activity have been reported by Singh and Nath (1975). Injection of cadmium chloride (3.2 mg/kg) into rats caused 89 percent inhibition of succinic dehydrogenase activity using liver and testis preparations, but enhancement of lactate dehydrogenase activity. Both enzymes were inhibited on cadmium addition _in vitro_.

A number of studies have been concerned with the influence of Cd on biochemical activity in discrete subcellular components. Membranes, in particular, are especially vulnerable to the effects of cadmium and other heavy metals. They mediate the transer of materials in and out of cells via active transport and exchange mechanisms that require initial complexing. Such complexing may be easily interfered with by the surface binding of metals.

An organelle that is also quite sensitive to the effects of cadmium is the mitochondrion. Since all of the enzymatic machinery required for cellular oxidation, including oxidative phosphorylation, sugars, amino acids, and fatty acids are located in the mitochondria, there are potentially a number of sites within the mitochondrion where cadmium may impart an effect. According to Berry _et al_. (1974), the ion is active at three places.

(1) It binds to sulfhydryl groups of enzymes necessary for electron transport from the citric acid cycle to the electron transport chain.

(2) It inactivates one or more enzymes necessary for the synthesis of adenosinetriphosphate (ATP).

(3) It binds to ATPase, the enzyme required for the conversion of ATP, or adenosine diphosphate (ADP), an important energy source in cellular reactions.

In the study of Suda _et al_. (1974), kidney mitochondria were isolated from rachitic chicks, and their activity in tritiated 25-hydroxy-Vitamin D_3 (^3H-25-OH-D_3) metabolism was studied as a function of added cadmium ion. As little as 2.5×10^{-5} M cadmium ion completely inhibited the biosynthesis of the active form of Vitamin D_3. This is in contrast to _in vivo_ studies in rats, where a Vitamin D-deficient diet also containing 300 ppm of cadmium chloride for 3 wk furnished significant amounts of 1,25-dihydroxy-Vitamin D_3 (1,25-$(OH)_2$-D_3). These and other data led the authors to conclude that metallothionein (discussed below) serves as a protective factor against this aspect of cadmium toxicity.

Diamond and Kench (1974) studied liver mitochondria from rats chronically poisoned with cadmium (i.p. injection, twice weekly, 1 mg/kg/wk). Mitochondria exhibited diminished respiratory control with progressive cadmium intoxication. Cadmium added _in vitro_ to mitochondria from exposed animals did not stimulate oxygen uptake, but control mitochondria respiring on succinate did show stimulation of oxygen utilization. While no pattern difference is seen between poisoned and control animals in reduced cytochromes, cadmium added _in vitro_ at levels greater than or equal to 10^{-4} M prevented subsequent reduction of the cytochromes. This appears to be indicative of a cadmium effect prior to electron transfer through the cytochrome system.

Kamata _et al_. (1976) showed, in an _in vitro_ study, that State III respiration with succinate in rat-liver mitochondria is strongly inhibited by cadmium. This inhibition is greater than for other heavy metals such as lead or mercury. At 0.5 to 3 micromolar cadmium, oxidative phosphorylation was decoupled, and State IV respiration was accelerated. _In vivo_, oral administration of cadmium (300 ppm in water) reduced the respiration control ratio and the P/O ratio but increased mitochondrial cytochrome a (+a_3) and cytochrome c (+C_1).

Stoll et al. (1976) have investigated the biochemical activities of hepatic nuclei and microsomes from rats given cadmium chloride (0.34 to 3.4 mg Cd/kg, i.p.). When cadmium was added to isolated hepatic nuclei, ribonucleic acid (RNA) synthesis was inhibited. When hepatic microsomes were preincubated to destroy messenger RNA (mRNA), the polyuridylic acid-directed incorporation of L-[^{14}C] phenylalanine was significantly inhibited by cadmium pretreatment; and such activity was inhibited in the same way when cadmium was added to preincubated microsomes from control animals.

In a related study by Norton and Kench (1977), cadmium administered to rats (2 mg Cd/kg/wk for 2 to 3 wk) caused inhibition of protein synthesis *in vitro* by isolated ribosomes in an amino acid-incorporating system.

Mego and Cain (1975) investigated the effect of cadmium on heterolysosome formation and function from the kidney and liver of mice. Pretreatment with cadmium inhibited proteolysis in liver particles 2 hr after i.p. injections of LD_{50} doses (4.3 mg Cd/kg), such inhibition becoming more pronounced up to 20 hr post-exposure. Kidney particles were less affected. Injections of cadmium also inhibited proteolysis of albumin in isolated liver heterolysosomes prepared 1 hr later.

Several studies have investigated the subcellular localization of cadmium. In one case, Popham and Webster (1976) employed a technique for the ultrastructural localization of cadmium in proximal tubule cells of mice consisting of precipitation of cadmium as the sulfide using ammonium sulfide after brief fixation in glutaraldehyde. In mice chronically exposed to cadmium (50 ppm in drinking water for up to 8 mo), cadmium was localized mainly in the apical vesicles, lysosomes, and cytoplasm of proximal tubular cells.

Hidalgo and Bryan (1977) used radioisotopic cadmium (^{115}Cd) to assess distribution of cadmium in rat liver after a single exposure (20 μ mol Cd/kg). The label was associated with the nucleus and the cytoplasmic fractions. The nuclear cadmium was more concentrated in non-histone proteins than in the histone proteins. Cytoplasmic cadmium was associated with two metal-binding protein subfractions.

In the report of Norton and Kench (1977), significant quantities of cadmium were found in purified ribosomes and enzyme preparations when cadmium was given to rats (2 mg Cd/kg/wk for 2 to 3 wk).

The cytotoxicity of cadmium as seen in cell-culture studies has been reported by several investigators. In this regard, Waters *et al*. (1975) have employed an *in vitro* system for assessing the cytotoxic effect of cadmium and other heavy metals using rabbit alveolar macrophages exposed in tissue culture for 20 hr. Of the various toxic substances assessed, cadmium was one of the two most toxic at metal levels below 3 mM, with cadmium reducing cell viability without lysis. Cadmium also caused a reduction in the activity of acid phosphatase, a lysosomal indicator enzyme and an active component of alveolar macrophages, in a manner that parallels decreases in cellular viability. On the basis of parallel morphologic evidence, the following sequence of damaging events is suggested by the authors: (1) retraction of normally extended pseudopodia, (2) appearance of surface structures, (3) smoothing of the plasma membrane, and (4) effacement of cell architecture.

An *in vitro* technique has been developed to assess alveolar macrophage function specific for phagocytosis (Graham *et al*., 1975) and determine the effect of various metal ions, including cadmium. This entails a double-viability stain to eliminate non-functioning dead cells from phagocytic measurement. Cadmium, at a concentration of 2.2×10^{-5} M, showed significant lowering ($p < 0.001$) of the phagocytic index (PI)

Using pulmonary alveolar macrophages, peritoneal macrophages, and polymorphonuclear neutrophils from the mouse, Loose et al. (1977) observed no significant alteration in their resting oxygen consumption when incubated in media containing cadmium salts. When heat-killed P. aeruginosa were added to the cell suspension, however, a significant depression in respiratory burst following phagocytosis was apparent and dependent on cadmium concentration, starting at 3.6×10^{-5} M. According to the authors, impairment of phagocytosis by cadmium ion may be associated with the known inhibitory action of this toxin on the ATPases of myosin and cell membranes. Altered phagocytotic activity by these cells may explain the enhanced bacterial susceptibility posed by cadmium, as reported by Cook et al. (1975a,b).

An in vitro investigation by Kawahara et al. (1975) involved cells from L-strain fibroblasts derived from the C^3H-strain mouse, cultured with YLH medium and supplemented with 10 percent bovine serum. A level of cadmium ion of 15.6 µg/ml medium was used. Severe changes were noted under an electron microscope: ribosomal disappearance, mitochondrial changes from waning of membrane and irregular arrangement of cristae to total disintegration, and a swollen and bead-like endoplasmic reticulum. The organellar damage appeared to be much worse than that from mercuric chloride.

Ozawa et al. (1976) monitored the differential susceptibility of L cells in the exponential and stationary phases to cadmium ion. L cells derived from mouse subcutaneous connective tissue were grown in Ham's F12 medium supplemented with 15-percent calf serum, 50 U/ml Penicillin G, and 50 µg/ml streptomycin. Cadmium ion was added on the first, second, and fourth days (exponential phase) and the ninth, eleventh, and twenty-second days (stationary phase) at a level to make a final concentration of 2.8 to 88.0 μM. The LD_{50} of cadmium ion for these cells in the two phases was 5.5 and 30.5 μM, respectively. Enhanced susceptibility in the exponential phase may be due to an increased cell membrane permeability. The corresponding cadmium contents of the cells in the two phases were 0.12 and 0.065 μg/10^6 cells.

2.3.2 Metallothionein

No discussion dealing with the subcellular metabolism and toxicity of cadmium would be complete without a consideration of the physiological role played by metallothionein. Metallothionein (the protein moiety thionein plus a complexed metal or metals) is a low-molecular-weight intracellular protein with a propensity for binding cadmium, zinc, mercury, copper, and to a lesser degree, certain other ions. It exists in at least two molecular forms. Structurally, cadmium binds to thionein through three sulfhydryl groups per metal atom, the sulfhydryl groups being available from the rather high cysteine content of the protein. While much in the way of metallothionein biochemistry has been reported, our interest is mainly centered on its function in the regulation of cadmium toxicity. An early review of metallothionein is presented in Friberg et al. (1974).

Cadmium-thionein and other metallothionein-like proteins have been isolated and studied from a number of organ systems of varous species, including man. Since metallothionein is an inducible protein, with its biosynthesis in liver and other organs being accelerated by challenging the organism with cadmium and certain other ions, much interest has centered on the role of metallothionein in mediating the movement and affecting the toxicity of cadmium.

While this protein may be involved in transport of cadmium in the blood, in organ distribution, and in excretion (Nordberg, 1972), questions have been raised as to whether metallothionein provides a protective function, as was first suggested by Piscator (1964), or whether this role is secondary to its regulation of zinc and/or copper metabolism.

In various experimental animals, pretreatment with a low dose of cadmium ion protects against a subsequent, usually fatal dose of the toxic agent (Parizek, 1957; Gunn _et_ _al_., 1968), since with repeated doses a larger portion of the dose accumulates in liver and kidney as metallothionein (Webb, 1972).

In the study of Leber and Miya (1976), mice exhibited tolerance to cadmium toxicity after pretreatment with either cadmium or zinc acetate. Cadmium doses of 1.0 and 3.2 mg/kg given 2 days before cadmium challenge resulted in LD_{50} values of 6.0 and 8.2 mg/kg respectively, versus a value of 4.5 mg/kg without pretreatment. Similarly, the LD_{50} value is roughly doubled (6.5 mg/kg) when pretreatment with zinc is carried out 12, 30, and 48 hours before cadmium exposure. The amount of hepatic metallothionein was seen to be proportional to pretreatment dosing.

Webb and Verschoyle (1976) reported that pretreatment of female rats with a low dose of cadmium ion provided defense against a subsequent, usually lethal dose of the metal and also induced the synthesis of hepatic cadmium-thionein. While this protection was at optimum one to three days after pretreatment, both the increased content and increased biosynthesis of cadmium-thionein persisted beyond this time. Using radioisotopic cadmium (^{109}Cd), these workers also noted that, although cadmium ion is bound more strongly by the apoprotein, thionein, rats in which the levels of zinc-thionein were elevated by starvation showed the same susceptibility to cadmium as animals on normal diet. This indicates that while synthesis of cadmium-thionein probably accounts for tolerance by animals of a larger quantity of cadmium given in multiple doses, Webb claims that neither preinduction of the protein nor zinc-thionein serves a protective function. This may be contrasted to the observation in the earlier study that zinc-thionein induced by zinc pretreatment does ameliorate lethality. As might be expected, accumulation of cadmium in the liver is greater under conditions of pretreatment, while uptake of the ion in other tissues (heart, spleen and pancreas) is unchanged.

In the related study of Probst _et_ _al_. (1977), a dose-dependent tolerance to acute cadmium toxicity was evidenced by elevated LD_{50} values in cadmium-pretreated mice. Also, hepatic metallothionein levels increased with the increase in pretreatment dosing. Since pretreatment at a level of 2.0 mg Cd/kg, but not at 0.6 mg/kg or 0.2 mg/kg, resulted in elevated LD_{50} and cadmium-binding capacity relative to controls, it appears that a minimum dose of cadmium must be exceeded in order to occasion sufficient induction of metallothionein to modify the acute toxicity of the metal (Probst, 1977).

The protective behavior of cadmium pretreatment was also studied by Squibb et al. (1976), who observed that rats pretreated with 20 mg Cd/kg followed by another oral dose of 100 mg Cd/kg showed greater uptake of cadmium by liver, kidney, and testis. At all time points (1, 3 or 5 hr), liver cadmium was associated entirely with metallothionein. In animals not given pretreatment, metallothionein-bound cadmium was not observed until 15 hr later. Radio-labeled cystein studies (^{35}S) showed that biosynthesis of the binding protein occurred following metal exposure. The observation that all of the cadmium in intestine was bound to metallothionein may suggest that the protein has a role in affecting cadmium absorption during low-level cadmium exposure.

Chen et al. (1975a) studied the synthesis and metabolic degradation of rat hepatic metallothionein stimulated by cadmium challenge. In regard to degradation of the protein, the half-life of 4.2 days observed after a single exposure to cadmium (subcutaneously, 26.7 μ mol/kg body weight) was not materially different from the value (4.9 days) observed after a second dosing, although liver cadmium content was doubled. Here, there is no stabilizing effect on the protein imparted by cadmium. Zinc, however, was lost from the metallothionein fraction at a rate similar to that of cystein [^{14}C]. Cadmium persisted in the liver-binding protein fraction up to 29 days post-injection and may do so in the face of observed protein breakdown by being released and immediately stimulating more thionein biosynthesis.

Cherian and Shaikh (1975) induced metallothionein in rats with cadmium, labeling the formed metalloprotein in vitro with either ^{109}Cd, ^{14}C or ^{35}S. After isolation from liver and subsequent intravenous administration to rats (at Cd levels of 10, 30 and 200 μg Cd), it was observed that tissue distribution of the radiolabeled ion in the metalloprotein was different from that given as the chloride (200 μg Cd). When given as cadmium-thionein, the deposition of cadmium in kidney was higher than in liver and a significant urinary excretion of the ion was observed when given as cadmium-thionein. Furthermore, the distribution and excretion of the thionein moiety was similar to that of cadmium.

Several reports have since appeared in the literature relating the comparative toxicity of cadmium-thionein to ionic cadmium when administered as such. Cherian _et_ _al_. (1976), for instance, isolated cadmium metallothionein from livers of metal-exposed rats, labelled the metalloprotein ^{109}Cd, and injected the material into a second group of rats. When compared with exposure to cadmium chloride, the organellar distribution of label from both forms in renal tubule cells was similar; but within 12 hours, degenerative changes were observed in the ultrastructure of renal tubule cells of animals dosed with the cadmium-thionein but not the cadmium salt. In a related study, Cherian _et_ _al_. (1978) fed cadmium to mice in the form of either cadmium chloride or cadmium-metallothionein labeled with ^{109}Cd. The inorganic salt was accumulated in the liver, while protein-bound cadmium appeared in the kidney. The extent of absorption in both forms was similar. These data are significant in terms of exposure of human populations to cadmium in diet. In particular, food-animal organs such as liver and kidney, which are high in heat-stable metallothionein-bound cadmium, may provide an unacceptably high level of cadmium in terms of human renal burdens of the element.

Further evidence that cadmium-thionein is involved in the pathogenesis of renal tubular cell injury is the study of Nordberg and Nordberg (1975). Cadmium-metallothionein, labeled with ^{109}Cd _in_ _vitro_, was injected into rats (1.6 μg Cd as either metalloprotein or $CdCl_2$). After 4 hr, over 80 percent of the injected dose was in the kidney when pure metallothionein was used.

Webb and Etienne (1977) observed that cadmium, when bound to thionein from either rabbit or rat liver, was 7 to 8 times more lethal to the rat than was ionic cadmium. Zinc-thionein was not only nontoxic, however, but protected the animals from a subsequent, usually fatal dose of the cadmium-thionein. As also noted above, cadmium-thionein accumulated in the kidney; its lethality was associated with severe tubular damage. Other data in this study suggest that parenteral dosing with cadmium-thionein is followed by renal tubular uptake, and ensuing breakdown of the protein moiety liberates cadmium in the directly toxic ionic form.

In summary, the literature dealing with the cadmium-metallothionein relationship rather conclusively demonstrates that (1) with relatively acute exposure to cadmium, metallothionein serves a protective function for the organism, while (2) in the long-term chronic exposure situation, cadmium bound to metallothionein may be in an inert form up to a certain level, but beyond that level is probably released in a systemically toxic form.

2.4 RESPIRATORY EFFECTS OF CADMIUM

A number of acute and chronic respiratory effects of cadmium have been documented in man and animals. Friberg _et_ _al_. reviewed the earlier literature in 1974.

2.4.1 Effects on Humans

In man, acute effects of cadmium via inhalation may not appear until some time after exposure, about 24 hours. Chief symptoms and signs are shortness of breath, general weakness, fever, and in extreme exposure cases, respiratory insufficiency with shock and death. These exposures are associated with pulmonary congestion and edema. Individuals surviving the exposure episode regain partial lung function but have a high probability of subsequently dying of chronic pulmonary insufficiency (Friberg _et_ _al_., 1974). It has been estimated that the pulmonary retention of 4 mg in man is fatal (Gleason _et_ _al_., 1969).

A recently reported case of fatal cadmium-fume pneumonitis (Patwardhan and Finckh, 1976) typifies the characteristics of the lethal form of acute cadmium intoxication. A welder spent the day welding handles to cadmium-plated drums. He went home at the end of the day showing no ill effects. Late that same evening, throat irritation developed and was followed by coughing, difficulty in breathing, fever and rigors. By the middle of the second day, he was severely dyspneic, cyanotic, febrile, and sweating. Impaired gait and speech were noted. Examination by X-ray showed heart enlargement, gross pulmonary edema, and elevated diaphragm. The patient expired about 3 days after exposure to occupational cadmium fumes. The lungs were voluminous, dark, congested and firm. Microscopic examination revealed degeneration; epithelial loss in bronchioles was present, and areas of regeneration were seen in which epithelial cells were spreading across the mucosal surface. Also present was diffuse congestion of alveolar capillaries with intra-alveolar proteinaceous exudate and shed alveolar lining cells and macrophages. Liver and lung cadmium values were 2.3 and 1.5 ppm, wet weight, respectively.

The chief pulmonary effect of chronic cadmium inhalation in man appears to be centrilobular emphysema and bronchitis arising after several years of occupational exposure to cadmium-oxide fumes, cadmium-oxide dust and cadmium-pigment dust (Eriberg _et al._, 1974). Furthermore, lung impairment is likely at cadmium oxide fume levels below 0.1 mg/m^3.

With respect to populations at large, it should be noted that while the added body burden of cadmium contributed by cigarette smoking has been established, the role of cigarette cadmium in a cause/effect relationship to chronic pulmonary disorders, as distinct from smoking, _per se_, has yet to be demonstrated.

Several reports have appeared dealing with the effect of cadmium salts *in vivo* and *in vitro* on human alpha-1-antitrypsin, the major proteinase inhibitor in human plasma, a deficiency of which is associated with chronic obstructive lung disease. Chowdhurdy and Louria (1976) reported a concentration-dependent decrease in both antitrypsin level and inhibitory capacity in response to added cadmium. No other heavy metal was seen to have this effect. Glaser *et al*. (1977), however, claim that this effect is an artifact due at least in part to the acid content of the cadmium-dosing solution. Chowdhurdy and Louria (1977) in turn claim that a pH effect can only be part of the answer, since their *in vivo* work with mice indicates that a similar response occurs where pH is not a factor. A second report which is even more significant regarding the effect of cadmium on α_1-antitrypsin is that of Bernard *et al*. (1977). Their results, using workers exposed to excessive amounts of cadmium and showing signs of cadmium intoxication, did not indicate any reduction of α_1-antitrypsin in the blood of these workers.

2.4.2 Animal Studies

The acute effects of cadmium on the lung have been studied in experimental animals using generated cadmium fumes or cadmium aerosols. In one relevant study, mice exposed to cadmium fumes (1.3 to 1.7 mg/m^3) for 1 hr were studied by Fukase and Isomura (1976), who observed that such treatment caused increased content of glutathione as well as increased enzyme activities of the peroxidative metabolic pathway in the lung.

Yoshikawa and Homma (1974) assessed the 50-percent lethal concentration (LC_{50}) of cadmium fumes in rats using a particle size of 0.2 μ and found the value to be 25 mg/m^3 for a period of 30 min. Retention of inhaled cadmium in the lung was 15 percent at a 30-min exposure level of 20 mg/m^3, and at 1 wk post-exposure 54 percent of the cadmium body burden was still retained in the lung.

Cadmium dust (1.1 mg/m^3 up to 4 wk) was seen by Watanabe et al. (1974a) to produce effects in rats that included septal interstitial pneumonitis and cell nuclear changes.

Hayes et al. (Strauss et al., 1976; Hayes et al., 1976) have carried out a series of inhalation studies in rats using a polydispersal cadmium chloride/saline aerosol. Using an aerosol of 0.1 percent cadmium chloride (4.5 μ, 10 mg Cd/m^3) for an exposure period of 2 hr, these workers (Strauss et al., 1976) found morphological evidence for acute lung injury by 24 hr post-inhalation. Examination by microscopy revealed multifocal damage in respiratory bronchioles. Ultrastructural studies showed:

(1) Type 1 cell edema occurred, with loss of plasma membranes, by 24 hr.

(2) By the second day, the number of Type 2 cells had increased.

(3) By day 3, the damaged alveoli were lined by cuboidal cells.

(4) By day 10, these cells had regained the appearance of Type 1 cells.

In a related study (Hayes et al., 1976) assessing biochemical aspects of lung injury in rats using the above aerosol-exposure model, this same group noted that by the fourth day after exposure the total lipid content and lactate dehydrogenase and G-6-PD activities had all doubled, coinciding with doubling of lung weight and total lung DNA content. Malate dehydrogenase activity was very high 1 hr post-exposure, followed by subsequent reduction to a level comparable to the other enzymes. With the exception of the effect on malate dehydrogenase, which is an index of mitochondrial injury, the biochemical responses appear to be nonspecific.

Adalis *et al*. (1977) studied the effect of cadmium on ciliary activity using isolated hamster tracheal rings and an organ-culture system. Statistically significant reductions in ciliary activity were seen at cadmium concentrations as low as 6 μM. Similarly, cilia from hamsters exposed to a cadmium chloride aerosol (2 μM, 2 hr, 50 to 1420 μg/m^3) were studied. In this case, the mean cilia-beating frequencies in all treatment groups were lower for recovery periods of 24 and 48 hr.

Gardner *et al*. (1977) have reported that cadmium inhalation (aerosol) also reduces the lung's ability to fend off microbial insults. Increase in mortality (15 to 70 percent) was observed in mice exposed to levels of 80 to 1600 μg/m^3 followed by streptococcal challenge. There was a marked decrease in the total number of alveolar macrophages recovered from lungs post-exposure, with a return to normal seen within 24 hr. Polymorphonuclear leucocytes increased dramatically by 24 hr after exposure, while lymphocyte numbers were unchanged. It is of interest to note the studies cited in the cytotoxicity section regarding the cell-culture studies of these same cells exposed to cadmium in a culture medium. Streptococci clearance from the lung was correlated with the mortality pattern.

Cadmium appears to affect the pulmonary tract even when the exposure is other than by inhalation. Miller *et al*. (1974) studied the effect of cadmium in rats exposed to dietary cadmium (17.2 μg/ml cadmium chloride; 6, 16 and 41 wk) in regard to the fine structure of connective tissue. After 6 wk of exposure, a general process of fibrosis was well established in sub-pleural tissue of the treated rats. Collagen fibrils were bundled.

There was increased density of the interstitial space merging into the basal lamina. An inflammatory response characterized by plasma cells and the deposition of the primary elements of fibrosis seem to be an early reaction to cadmium, progressing rapidly over a period of 16 wk, leaving the interstitium thickened at the lung periphery. The sub-pleural elastic layer showed focal disruption. Few polymorphonuclear leucocytes were seen. No abnormal fiber types were present after 16 wk of exposure. After 41 wk of exposure, there was a slow progression of the fibrosis. It is possible at least part of these effects are related to cadmium effects on copper metabolism via interference with copper enzymes (O'Dell et al., 1966; Murthy et al., 1972).

In the exposure study of Stelzner et al. (1975), intratracheal injection of 10 mM cadmium chloride resulted in degeneration of bronchial epithelium and widespread alterations in the lung. Regeneration of bronchial epithelium occurred by 8 wk, while the distal lung showed areas of emphysema and extensive scarring. Histochemically, there was a return by 8 wk to the normal pattern of staining for lysosomal enzymes. Ultrastructurally, rapid regeneration and ciliogenesis in bronchi and denuded basement membrane were seen, proceeding to hyperplastic Type II cells and layered membranous cells in the distal lung.

2.5 RENAL EFFECTS OF CADMIUM

The effects of both acute and chronic exposure to cadmium on the renal system have been noted in the literature from experimental animals and from clinical and epidemiological data. Both acute and chronic aspects of renal toxicity of cadmium have been reviewed by Friberg et al. (1974), Nordberg (1976), and Kawai (1976).

The most typical feature of chronic cadmium intoxication is renal damage, and thus, the kidney may be considered the critical organ in chronic exposure (Nordberg, 1976).

In particular, cadmium affects the reabsorption function of the proximal tubules, with an early sign of this effect being an increase in the urinary excretion of low-molecular-weight proteins--tubular proteinuria. The proteins, occurring in plasma, are normally almost totally reabsorbed, but the cadmium-injured kidney is less able to achieve complete resorption.

Later effects are aminoaciduria, glucosuria, and phosphaturia (Piscator, 1966a). Disturbances in kidney function are also manifested by effects on bone and mineral metabolism, via increased excretion of calcium and phosphorus. Early reports have described kidney stones in Swedish workers (Friberg, 1950) and osteomalacia in French workers (Nicand et al., 1942), as well as certain populations in Japan exposed to dietary cadmium (Friberg, et al. 1974). According to Piscator (1966a), once tubular proteinuria is induced, it is essentially irreversible.

2.5.1 Animal Studies

In experimental animals, the level of kidney damage due to chronic cadmium exposure is dose-related, from early-detected degenerative changes in the proximal tubules passing on to interstitial edema, glomerular capsule thickening, and basement membrane fibrosis as exposure continues. It is possible that renal vasculopathy accounts for the interstitial and fibrotic sequelae, while cadmium acting on the renal tubule directly may account for tubular changes (Kawai et al., 1976).

According to Kawai et al. (1976), there are morphologically distinct features of acute cadmium insult to the kidney in experimental animals in contrast to chronic exposure. In the acute case, hydropic swelling and acidophilic necrosis are seen, while tubular atrophy characterizes the chronic case. Pronounced edema in the surrounding interstitium is present, eventually resulting in interstitial fibrosis and nephrosclerosis at a later stage. Acute lesioning in tubular epithelium may be seen and is dose dependent. These observations suggest that vascular injury probably plays a major role in acute nephropathy.

In the studies of Kawai and coworkers (Kawai and Fukuda, 1974; Kawai et al., 1974) involving chronic cadmium poisoning in rats (10 to 200 ppm cadmium in tap water for 8.5 to 18 mo), tubular atrophy with interstitial edema was found in the kidneys of rats receiving 100 ppm cadmium or greater; and slight lesioning was observed in some animals at 50 ppm. The corresponding kidney metal levels were 150 and 37 μg/g wet weight, respectively. Cadmium excretion from kidney apparently increases as renal injury becomes more severe.

Itokawa et al. (1974) studied two groups of rats that received 50 μg Cd/g of diet with and without sufficient calcium for a period of 4 mo and observed considerable renal injury. The tubular epithelium was desquamated and vacuolized, and there was necrosis and partial hyalinization in glomerular capillaries with adhesions between the Bowman capsule and glomerular capillaries.

After 16 wk of feeding, Nomiyama (1975) observed that rabbits given 300 μg Cd/g in food began to show increased urinary amino acid excretion, concomitant with increases in certain enzymes. After 38 and 42 wk, total protein and sugar levels respectively were elevated, but amino acid levels after 30 wk were similar for both control and exposed animals. The corresponding kidney cadmium levels for these time points were 200 and 300 μg Cd/g wet weight.

Axelsson and Piscator (1966) showed that in the rabbit proteinuria appeared before aminoaciduria. In man, proteinuria is certainly an earlier sign than aminoaciduria.

Suzuki (1974) found that, in rats exposed to low levels of cadmium for 16 wk, a kidney cortex level of 225 μg Cd was associated with proteinuria and a dramatic increase in urine cadmium.

Gonick et al. (1975), in their studies of cadmium-induced experimental Fanconi syndrome in female rats, gave repeated injections of cadmium ion (0.6 mg Cd/kg, i.p.) until the onset of glycosuria (24 days). By 2 days after the occurrence of glycosuria, the Fanconi syndrome was essentially complete in terms of: urinary volume increases; increased excretion of protein, glucose, and α-amino nitrogen; and increased fractional excretion of sodium, potassium, calcium, magnesium, and phosphate. Also, renal cortical Na^+-K^+-ATPase activity was reduced to less than half that of controls with reduction in ATP levels. The effect on this enzyme activity was consistent with ultrastructural evidence, i.e., extensive loss of basal membrane infoldings, the principal site of the enzyme's activity. Likewise, reduction in ATP levels paralleled evidence of alterations in the mitochondria.

Fowler et al. (1975) studied the effects of chronic cadmium administration on rat renal vasculature using low and normal calcium diets. Both diet groups of rats were exposed to cadmium via drinking water (0.2 to 200 ppm cadmium, 6 or 12 wk). Constriction of smaller renal arteries, mild dilation of larger arteries, and a diffuse scarring of peritubular capillaries were observed at 6 wk at even low doses (2 and 20 ppm Cd), with arterial constriction appearing to subside by week 12. These changes would indicate a decrease in effective renal circulation with time. While variation in calcium intake did not appear to influence the vascular effects studied, increased renal depositon of cadmium in the low-calcium rats was observed.

Since chronic cadmium exposure occasions renal tubular dysfunction, one might expect that this in turn would influence the metabolism of Vitamin D. In the section dealing with subcellular aspects, it was noted (Suda _et_ _al_., 1974) that _in_ _vivo_ formation of 1,25-dihydroxy-vitamin D_3 was not markedly altered by a diet containing cadmium but that was Vitamin D deficient.

In the study of Lorentzon and Larsson (1977), however, in which rats were chronically exposed to cadmium in drinking water (0.22 and 0.69 m mole Cd/1) for a period of 3 mo and were on either normal or low-calcium diets, both levels of cadmium exposure led to reduced formation of 1,25-dihydroxy-Vitamin D_3 in kidneys as well as serum and liver, with the higher level yielding only minute amounts in the kidney. Even at the higher dose, there was only a slight effect on reduction of the conversion product with low calcium intake. Further, cadmium exposure showed a shift in Vitamin D metabolism over to formation of the less active metabolite 24,25-dihydroxycholecalciferol.

Pierce _et_ _al_. (1977) investigated the use of urinary enzyme activities as markers for the nephrotoxicity of cadmium in the marmoset and rat.

Excretion of urinary enzymes in rats that had been dosed by subcutaneous (s.c.) injection (1.5 mg/kg/day) remained at control-animal levels to day 15. An increase of β-glucosidase activity occurred and continued to rise until the experiment was terminated ($p < 0.01$). N-acetyl-β-glucosaminidase activity increased by day 18. With marmosets, oral exposure to cadmium was without effect on urinary enzyme levels, but s.c. injection (6 days, 5 mg/kg/day) gave rise to an increase in enzyme activity by day 2 in the case of N-acetyl-β-glucosaminodase.

2.5.2 Human Studies

A number of studies have been directed to the chronic nephrotoxicity of cadmium in man, particularly cadmium workers and Japanese populations receiving environmental exposure via rice, fish, and water contamination. The earlier clinical and epidemiological studies have been reviewed by Friberg, et al. (1974).

Current investigations have included assessment of the extent and nature of the tubular derangement seen in man with chronic cadmium exposure, including the occurrence of proteinuria. In chronic cadmium poisoning in man, the urinary proteins vary in molecular weight from 10,000 to 200,000 with more than half of the total protein being smaller than albumin. The globulin fraction includes α_2-β_2- and α globulins, β_2-microglobulin, retinol-binding protein, and α-globulin L chains.

Several studies have been directed to characterizing the nature of urinary proteins excreted in excess in response to chronic cadmium exposure. Peterson and Berggard (1971), for example, reported that retinol-binding protein (RBP) appears in human urine as a result of cadmium poisoning, and later investigators have studied the nature of the protein as well as its occurrence in other species in response to cadmium challenge.

Clark and coworkers (1975) in their studies of tritium-labeled retinol show that cadmium-treated rats excreted excess amounts of a protein bound to retinol or a retinol metabolite and having a molecular weight of about 4600.

Muto and coworkers (1976) exposed rabbits to cadmium (0.8 and 1.5 mg/kg body weight, s.c. 5 times per wk) and found a large excretion of retinol-bound protein of molecular weight 20,000. Though similar to human RBP (Kawai _et_ _al_., 1971, 1972) they are immunologically distinct.

Perhaps a more significant urinary protein in terms of its being an index of renal damage induced by cadmium is β_2-microglobin. The biochemical and diagnostic aspects of this protein have been reviewed by Kjellström and Piscator (1977).

Piscator (1966b,c) found relatively high levels of the plasma protein β_2-microglobulin in the urine of cadmium workers, and Berggard and Bearn (1968) subsequently isolated and characterized this protein from cadmium-worker urine.

In the normal kidney, reabsorption of β_2-microglobulin is essentially complete: 99.9 percent reabsorption (Johansson and Ravnkov, 1972; Evrin and Wibell, 1972). According to Evrin and Wibell (1972), 100 μg is excreted daily via the normal kidney.

Coupling of the known data regarding the renal biochemistry of β_2-microglobulin with its increased excretion in cadmium exposure indicates that levels of this protein are rather good indicators of tubular proteinuria induced by cadmium, and efforts have been made to evolve both good quantitative measurements of the protein and baseline levels for diagnostic purposes. Furthermore, the much higher relative increase in β_2-microglobulin excretion than in total protein levels suggested that β_2-microglobulin analysis may be the most sensitive method of detecting the early stages of cadmium-induced renal tubular injury.

Of the various methods for quantitative assessment of this protein, the radioimmunoassay technique of Evrin et al. (1971) appears to be the most sensitive (2 µg/l), having a sensitivity about 50 times above that required for normal urine levels, about 100 µg. Details of the analysis have been reviewed (Kjellström and Piscator, 1977).

A number of epidemiological studies have been carried out using β_2-microglobulin measurement to assess proteinuria (Kjellström et al., 1977a,b; Kojima et al., 1977). The frequency distribution of individuals in normal groups was log-normal. Geometric average values of β_2-microglobulin in the general population range from about 50 to 100 µg/urine, while excretion levels in excess of 200 µg/l may be considered to be abnormal.

The dose-response relationship between increases in urinary excretion of this protein and cadmium exposure are evidenced by the data of Kojima et al. (1977) and Kjellström et al. (1977a).

In a number of cadmium-exposed areas in Japan, proteinuria has also been regarded as a manifestation of cadmium poisoning of the general population. These studies have been extensively reviewed and evaluated by Friberg et al. (1974) and by Shigematsu (1975), and particular attention has been given to Itai-Itai (Ouch-Ouch) disease, a condition embodying a number of toxic effects of cadmium and representing a classic case of environmental pollution in an industrialized society having severe consequences for the individuals involved. Itai-Itai disease is essentially cadmium-induced renal tubular dysfunction in a nutritionally-deficient population, leading to osteomalacia and osteoporosis. Most of the victims were post-menopausal women who had given birth to several children and had a history of calcium and vitamin D deficiency.

Itai-Itai disease was first found in Fuchu in Toyama Prefecture where rice fields irrigated by the Jintsu River were contamininated by waste products from a mine. As cited by Friberg et al. (1974), proteinuria and glucosuria were more prevalent in the Itai-Itai disease belt than in a control area.

Presently, a large amount of data has been collected from parts of Japan other than Fuchu where cadmium exposure has been suspected. Methods of assessment of proteinuria vary in the study areas, however; and this may play a role in the fact that findings of different proteinuria studies are at variance with each other.

In many of the cadmium-polluted areas for which age-related prevalence of proteinuria was amenable to calculation (such as the areas of Fuchu and Tsushima), there is a substantial increase in prevalence with age; and in Fuchu the causal role of cadmium in this relationship is apparent. Furthermore, the population in many of the polluted areas showed enhancement of proteinuria with age which was significantly different with control populations.

In a recent report (Shiroishi et al., 1977) detailing the results of a joint Japanese-Swedish study of the nature of cadmium-induced renal changes in individuals with Itai-Itai disease, as assessed by β-microglobulin excretion, it was determined that proteinuria in Itai-Itai disease is tubular. In particular, β_2-microglobulin excretion, an index of tubular injury, was found to be over 100 times higher than in a reference population.

Epidemiological aspects of cadmium-polluted areas of Japan are discussed in a later section dealing with epidemiological studies.

2.6 THE CARDIOVASCULAR SYSTEM

This section will consider mainly the major aspect of cadmium's effect on the cardiovascular system: hypertension. A sizable body of data exists regarding the induction of hypertension in experimental animals in response to chronic cadmium exposure. While the cause/effect relationship of cadmium to experimentally induced hypertension appears to be well established, the issue of the role of cadmium in the etiology of human hypertension still remains to be resolved.

2.6.1 Animal Studies

Perry (1976) and Friberg *et al*. (1974), have critically reviewed the earlier literature with regard to cadmium-induced hypertension in experimental animals such as the rat. The most relevant animal model for assessment of cadmium-induced hypertension is that employing oral exposure of the toxic element. Schroeder and Vinton (1962) first reported hypertension in animals fed cadmium, and this was confirmed by Perry and Erlanger (1971, 1974) and Sorenson *et al*. (1973).

Perry *et al*. (1977b) have recently reported that cadmium concentrations as low as 0.1 ppm in drinking water have induced the same degree of hypertension as the standard 5 ppm dose of cadmium; moreover, occasional subpopulations of "responders" have had a marked increase in pressure (Perry *et al*., 1978). In addition, simultaneous feeding of lead and cadmium can markedly augment cadmium-induced hypertension (Perry *et al*., 1977a).

The level of hypertension noted with chronic oral exposure, while statistically significant, is not great; and it is apparent from the literature that, in addition to a dosing regimen of a low cadmium level (5 ppm) in drinking water, other experimental details are important in observing the effect.

Frickenhaus _et_ _al_. (1976) exposed rats to cadmium sulfide in their diets (26 mg Cd S/kg diet and 52 mg CdS/kg diet) for 3 mo, at which time no significant changes in blood pressure were seen, although the levels of cadmium ingested may have exceeded the lower exposure levels in the work described above. In this connection, Perry _et_ _al_. (1977a) point out that hypertension in animals appears to be associated with a particular level of renal cadmium or a particular zinc-cadmium ratio, and that deviation in level up or down may cause the effect to disappear.

Parenteral adminstration of cadmium occasions acute hypertension in rats (Perry and Erlanger, 1971; Schroeder, 1967), rabbits (Thind _et_ _al_., 1970), and dogs (Thind, 1973). While the hypertension caused by low-level cadmium feeding is moderate and permanent, hypertension from cadmium injection is transitory.

Thind (1974) studied blood-vessel wall characteristics in experimental hypertension induced by parenteral cadmium. Utilizing _in_ _vitro_ techniques, the vascular reactivity and elasticity of blood vessels from rabbits and dogs exposed to cadmium were measured. It was found that the vascular reactivity of rabbit aorta to angiotensin was significantly reduced in cadmium-treated animals, while hypertensive dog carotid artery was less responsive to angiotensin, norepinephrine, and serotonin. Furthermore, the hypertensive dog carotid artery developed significantly lower passive elasticity modulus.

In a related study, Thind and Fischer (1975) measured cadmium and zinc distribution in cardiovascular tissue of cadmium-treated and normal dogs. Cardiovascular tissue levels of cadmium in both groups were high in peripheral and smaller arteries and myocardium. The distal mesenteric artery, mesenteric artery branches, main renal artery, and coronary arteries, however, tended to accumulate cadmium while zinc levels were highest in the mesenteric artery branches. Kopp et al. (1978) using rats exposed to 5 ppm cadmium for 24 months found (a) depressed myocardial excitability, (b) decreased high energy phosphate in the heart, and (c) morphologic changes in cardiac muscle.

Thind (1973) found an approximately seven-fold increase in renin activity of generated angiotensin I following cadmium treatment in dogs. Perry and Erlanger (1973) reported an increase in plasma renin activity in cadmium-fed rats.

Porter et al. (1975), in studies of rats given cadmium, failed to find elevated blood pressure but noted that the treated animals evidenced decreased blood-pressure responses to norepinephrine, acetylcholine, isoproterenol, and atropine. Aortic strips from the animals also showed reduced reactivity to angiotensin, epinephrine, barium, and tyramine. These data suggested to the authors that production of hypertension and desensitization of vasculature to vasoconstrictors and vasodilators may be unrelated biological events.

The effects of low dietary cadmium on blood pressure and on sodium, potassium, and water retention in growing rats were investigated by Doyle et al. (1975). Sodium retention was greater in both male and female rats fed cadmium. There was a transitory greater retention or loss of potassium in males and females, respectively, which abated by 330 days, although water retention was greater in treated animals at about the same time. No effect on blood pressure was seen, however. The absence of induced hypertension in this study was ascribed to differences in zinc in the diet, with zinc content being only a fraction of that used in the Perry and Schroeder models (*vide supra*) and other dietary differences as well.

2.6.2 Human Hypertension

As noted above, the case for cadmium as a factor in human hypertension is not clear-cut, and studies relating to this issue are discussed in the Human Epidemiology Section (3.5).

2.7 EFFECTS OF CADMIUM ON REPRODUCTION AND DEVELOPMENT

An extensive literature documents cadmium effects on the gonads, associated organs, and other aspects of reproduction and development, as reviewed by Fleischer *et al*. (1974), Friberg *et al*. (1975), and NIOSH (1976). Many of the more dramatic effects reported, however, have been obtained with injections of the metal at relatively high dosage levels; this has led to questions about the environmental relevance of such findings. Other research has focused on: (1) mechanisms of action by which the toxic effects are exerted, (2) whether such effects occur at lower, environmentally encountered exposure levels and via relevant exposure routes, and (3) whether comparable effects occur in occupationally or environmentally exposed humans.

2.7.1 Testicular Effects

Induction of acute testicular necrosis by cadmium has attracted considerable attention in the literature on experimental animal models, but is of questionable relevance in assessing the impact of environmental cadmium exposure on humans. In early studies (Parizek and Zahor, 1956; Parizek, 1957), a single subcutaneous (s.c.) injection of cadmium chloride at high doses (2.2 to 4.5 mg Cd/kg) was found to cause severe testicular damage in rats and mice. Within a few hours after cadmium injection, histologically detectable testicular changes such as interstitial edema occurred and progressed to extensive necrosis of the testes by 48 hr. Resorption of testicular tissue occurred by 10 days post-injection, and weights of accessory sex organs, seminal vesicles, and prostate glands were reduced. In a later study, Mason et al. (1964) injected a wider range of cadmium chloride doses (0.51 to 6.8 mg Cd/kg) s.c. into male rats and found the lowest effective dose to be 0.85 mg/kg.

The role of the testicular vasculature in determining cadmium effects on the testes has been one issue dealt with extensively in regard to characterizing mechanism(s) by which the metal damages male gonads. Much attention, for example, has been directed to whether cadmium-induced testicular necrosis results from a direct action of cadmium on the seminiferous tabule epithelium or occurs secondarily as a consequence of a primary damaging effect on the testicular vasculature. The case for the primacy of vascular damage has been well-argued in numerous individual research reports and several general review articles (e.g., Gunn and Gould, 1970; Friberg et al., 1975) and that view is the currently most widely accepted one in the field.

Arguments for the primacy of vascular effects underlying cadmium-induced testicular necrosis gained credence, in part, by virtue of variations in susceptibility of different species. It was first well-established that mammalian species possessing scrotal testicles were susceptible to the effect, since virtually all such species tested show marked acute testicular necrosis following a single systemic injection of cadmium. Such susceptible species are listed in Table 2-2. In contrast, several non-scrotal species with abdominal testes, as listed in Table 2-2, appear to be resistant to the induction of testicular necrosis by cadmium. That factors beyond vascularization patterns are important, however, is suggested by: (1) demonstration of susceptibility among some non-scrotal species listed in Table 2-2, and (2) demonstration of variations in susceptibility between strains within the same scrotal species (Gunn *et al*., 1965; Taylor *et al*., 1973).

Other evidence supports the view that cadmium causes testicular necrosis via a primary effect on testicular vasculature. This includes ultrastructural studies demonstrating: (1) signs of cadmium-induced increases in vascular permeability in testes (Clegg and Carr, 1967), (2) evidence of pinocytotic activity in testicular capillary endothelial and perivascular cells as well as loosened endothelial desmosome junctional complexes and signs of microhemorrhaging (Berliner and Jones-Witters, 1975), and (3) changes in intratesticular capillary endothelial cell junctions leading to separation of endothelial cells (Fende and Niewenhuis, 1977). Also, Koskimies (1973) showed that serum protein increased in rete testis fluid within 10 min after cadmium injection, but not in seminiferous tubule fluid until 2 hr.

Additional studies have focused on biochemical mechanisms possibly underlying cadmium-induced testicular damage. For example, the activity of carbonic anhydrase (CAH), a zinc-containing metalloenzyme, was decreased in testes after cadmium administration; and inhibition of CAH was taken to be

Table 2-2. SPECIES VARIATIONS IN SUSCEPTIBILITY TO CADMIUM-INDUCED TESTICULAR NECROSIS

Species tested	Testicular damage susceptibility	Reference
Scrotal species		
Rat	(+)	Parizek (1957)
Rat	(+)	Mason *et al*. (1964)
Mouse	(+)	Parizek (1957)
Mouse	(+)	Gunn *et al*. (1965)
Guinea pig	(+)	Parizek (1960)
Rabbit	(+)	Kar and Das (1962)
Gerbil	(+)	Ramaswami and Kaul (1966)
Gerbil	(+)	Berliner and Jones-Witters (1975)
Hamster	(+)	Girod and Dubois (1976)
Dog	(+)	Chatterjee and Kar (1968)
Dog	(+)	Donnelly and Monty (1977)
Goat	(+)	Kar and Das (1962)
Monkey	(+)	Kar (1961)
Non-scrotal species		
Suncus	(-)	Dryden and McAllister (1970)
Fowls	(-)	Johnson *et al*. (1970)
Frog	(-)	Chiquoine (1964)
Toad	(-)	Biswas *et al*. (1976)
Toad	(+)	Chiquoine and Sunzeft (1965)
Doves	(+)	Maekawa *et al*. (1964)

Table 2-2. SPECIES VARIATIONS IN SUSCEPTIBILITY TO CADMIUM-INDUCED TESTICULAR NECROSIS (CONTINUED)

Species tested	Testicular damage susceptibility	Reference
Fish	(+)	Maekawa and Tsunenari (1967)
Fish	(+)	Sarkar and Mondal (1973)
Fish	(+)	Tafanelli (1972)
Brook trout	(+)	Sangalong and O'Hallran (1973)

important in the etiology of cadmium-induced testicular necrosis (Johnson and Walker, 1970). Subsequent work reported by Alsen et al. (1976), however, provides strong evidence against this. As for other research attempting to identify particular proteins as pathogenic targets for cadmium in the testes, that of Chen et al. (1974) revealed two cadmium-binding moieties corresponding to proteins of molecular weights (MW) of 10,000 and 30,000 in the soluble fraction of whole testes; and Chen and Ganther (1975) later provided evidence for involvement of the 30,000 MW protein in the pathogenesis of testicular necrosis. This, however, is not supported by the more recent data of Prohaska et al. (1977). Lastly, Omaye and Tappel (1975) demonstrated reductions in plasma and testicular glutathione (GTH) peroxidase activity that they hypothesized to be important in mediating cadmium-induced testicular necrosis.

Certain data suggest that some cadmium-induced degenerative changes might occur secondarily to damage androgen-producing (Leydig) cells of the testes. Such data include the demonstration after cadmium treatment of: (1) decreased plasma levels of androgens (Chandler et al., 1976; Saksena et al., 1977), and increased testicular cholesterol levels indicative of decreased androgen production by the testes (Dixit et al., 1975); (2) alterations of cyclic AMP metabolism in the primary and secondary reproductive organs of the male rat consistent with reductions in testosterone (Sutherland et al., 1974); (3) evidence of Leydig-cell necrosis or reductions in metabolic activities in those cells (Girod and Dubois, 1974, 1976; Dixit et al., 1975); (4) signs of hyperplasia of gonadotropic cells in the anterior pituitary (Girod and Dubois, 1974, 1976), as well as increases in plasma levels of leuteinizing hormone (LH) (Chandler et al., 1976) and (5) autoradiographic localization of cadmium in testicular interstitial tissue (Nordberg and Nishiyama, 1972).

Chandler et al. (1976) observed changes in the ultrastructural integrity of the lateral prostate of the rat as early as one day after cadmium injections, too soon for decreases in circulating testosterone to have occurred. This suggests that cadmium may also exert a direct influence on the prostate before any further effects of reduced androgen levels are manifested. In addition Nordberg (1975) found that morphological changes in the seminal vesicles indicative of reduced testosterone levels occurred as a result of chronic exposures to doses of cadmium too low to produce alterations in testicular weight or histology, suggesting that cadmium can also exert effects on testosterone-producing testicular cells before necrosis occurs after vascular damage. Further support for this possibility is gained from another observation by Nordberg and Piscator (1972) on chronic cadmium doses below those producing testicular necrosis causing a significant decrease in the protein excretion of male mice before the onset of renal tubular dysfunction. Since the usual cadmium-induced proteinuria in mice was previously shown to be testosterone-dependent (Thung, 1956; Finlayson et al., 1965), the decreased production of testosterone was hypothesized as being an early effect of long-term cadmium exposure.

In view of the above results, much remains to be clarified concerning mechanisms by which acute high doses of cadmium cause testicular necrosis. Of greater importance here, however, is the issue of whether or not more chronic, lower-level exposures to cadmium cause significant morphological or functional changes in the testes.

Piscator and Axelsson (1970) reported that 0.5 mg Cd/kg doses of cadmium chloride, when administered subcutaneously to rabbits 5 times per week for 24 wk, caused no macroscopically or microscopically evident testicular changes but did cause marked kidney damage. In another study, Nordberg (1971) demonstrated that single, subcutaneous (s.c.) injections of cadmium chloride at 1 mg Cd/kg caused complete testicular necrosis in CBA mice, while single doses of 0.25 to 0.50 mg Cd/kg caused little or no damage to the testes. After administration of such doses 5 days/wk for 6 mo, no significant testicular changes were apparent at the 0.25 mg/kg dose level and only slight changes were evident at the 0.50 mg/kg level. This occurred despite the fact that testicular cadmium levels in these animals were 6 to 7 ppm, i.e., approximately 20 times as high as the levels (0.3 ppm) found to exist in the mice experiencing severe testicular necrosis after a single 1.0 mg Cd/kg injection. Repeated injections of 0.25 mg/kg doses, to stimulate metallothionein synthesis, prevented the induction of testicular necrosis by a 1.0 mg Cd/kg dose administered later. Also, no testicular necrosis occurred after injections of cadmium (1.1 mg Cd/kg) partially bound to metallothionein. When the same chronic dosage regimen as the first one used in the Nordberg (1971) study was employed in a subsequent experiment on renal effects, Nordberg and Piscator (1972) found that CBA mice receiving s.c. injections of 0.25 to 0.5 mg Cd/kg, 5 days/wk for 6 wk, developed signs of kidney damage.

Considered together, the above results appear to indicate that testicular damage does not occur after repeated administration of cadmium compounds at doses causing only slight or no kidney malfunction. Other data suggest, however, that more subtle testicular effects may occur in the absence of clear-cut kidney damage. Nordberg and Piscator (1972), for example, found a significant decrease in protein excretion before the onset of renal tubular dysfunction resulting in marked proteinuria, and Nordberg (1975) demonstrated effects on the seminal vesicles in the absence of changes in testicular weight or histology after chronic cadmium dosing that produced little renal dysfunction. Thus, even in the absence of demonstrable morphological damage to the testes, biological changes suggestive of probable altered testicular function were detected at cadmium exposure levels below or equal to those producing signs of relatively slight renal damage. Whether any such subtle testicular effects occur with chronic low-level cadmium exposure remains to be demonstrated, however, since moderately high acute doses of cadmium were used in the above studies.

In regard to dietary cadmium exposure, very low oral cadmium doses were reported to have been used as part of a joint Soviet-American project, as reported by Russian workers (Krasovskii et al., 1976). Chronic oral administration of cadmium chloride to adult male rats at four dose levels (control, 0.00005, 0.0005, and 0.005 mg Cd/kg) was achieved by cadmium concentrations of 0, 0.001, 0.01 and 0.1 mg/l, respectively, in the drinking water. At dose levels as low as 0.0005 mg/kg, numerous statistically significant gonadotoxic effects were reported to have occurred in conjunction with other, more general toxic effects. The Russian findings, which are difficult to evaluate adequately from their published description, must be viewed with caution, however, in view of unusually high blood cadmium levels reported for their control (70 µg Cd/l) and cadmium exposed animals (> 85 µg Cd/l) and in view of the cadmium doses used being far less than those likely to be present in food.

American phases of the same Soviet-American cooperative project have not yielded much evidence of testicular damage. Dixon et al. (1976) reported that possible "subtle reproductive effects" of cadmium were assessed in male rats exposed orally to cadmium chloride at concentrations of 0, 0.001, 0.01, or 0.1 mg/l in the drinking water, yielding estimated maximum doses of 14 µg/kg/day. Randomly selected animals were taken for study after 30, 60 and 90 days of exposure. Using a variety of evaluations, no significant differences were observed between control and cadmium-exposed animals at any dose level or exposure time. Nor were any significant general toxic effects obtained with a variety of clinical serum chemistry tests.

In another study, Loeser and Lorde (1977a) reported that cadmium chloride fed to groups of 20 male and 20 female rats over a period of 3 mo in concentrations of 0, 1, 2, 3, 10, and 30 ppm caused no histopathological signs of damage in the gonads or any other organs. Similarly, no significant effects were observed after the administration of the same doses of cadmium chloride for 3 mo to groups of 2 male and 2 female beagle dogs each (Loeser and Lorke, 1977b).

The Loeser and Lorke (1977a,b) and Dixon et al. (1976) results raise serious questions about cadmium having significant effects on male reproductive organs or functions when administered chronically at low dose levels. Still, since little or no data were reported on tissue levels of cadmium achieved in those studies, it is difficult to place them in perspective in relation to cadmium exposures known to produce other types of damage, e.g., renal dysfunction. Also, it remains to be assessed as to whether longer periods of exposure at the dose levels used might not produce significant testicular effects.

2.7.2 Ovarian Effects

Stimulated in part by findings of testicular necrosis in rodents after exposure to high doses of cadmium, several early studies have analogously focused on the effects of high-dose cadmium exposures on the ovaries of female rodents. Kar and coworkers (1959) exposed female rats, 6 to 8 wk old, to cadmium chloride via subcutaneous injections of 10 mg Cd/kg and found some acute ovarian effects. More specifically, although ovarian and uterine weights were not significantly altered, the rate of follicular atresia was clearly affected. Medium- and large-sized follicles were initially damaged, as indicated by signs of atrophy among granulosa cells and ova, followed by complete destruction of follicles of all sizes by 48 hr postinjection. In addition, the normal response of the ovaries to exogenously administered gonadotropins was blocked, suggesting a possible interference of cadmium with actions of endogenous pituitary factors on the ovaries. In a later study, Kar _et_ _al_. (1960) demonstrated that simultaneous injections of zinc or selenium along with cadmium prevented the ovarian damage otherwise obtained with cadmium alone. This is analogous to preventive effects of zinc and selenium against cadmium-induced testicular necrosis.

Evidence for cadmium-induced ovarian damage of the type described by Kar _et_ _al_. (1959) has not been universally obtained by other workers. In that regard, Gunn _et_ _al_. (1961) did not detect any pathological changes in the female reproductive tract or any other major organs in rats of another strain treated with 0.03 mM/kg of cadmium chloride; nor did Der _et_ _al_. (1977b) observe any pathologic or abnormal histology of ovary or uterus after daily intramuscular injections of 50 or 250 µg $CdCl_2$ in adult Wistar female rats for 54 days, although persistent diestrus was seen in the 250 μg dose animals. On the other hand, very distinct gross and morphological correlates of antigonadal effects were observed by Kaul and Ramaswami (1970) in the female gerbil. After a single subcutaneous injection of either 0.22 mg Cd/kg in immature animals or 0.45 mg/kg in mature animals, considerable reductions in the weight of the oviduct in both the immature and adult female gerbils were seen, and histological examinations revealed widespread follicular atreasia and extensive ovarian hemorrhages. No evidence exists, however, for the induction of such ovarian damage by cadmium with lower-level exposure by inhalation or ingestion.

2.7.3 Embryotoxic and Teratogenic Effects

Considerably more information than that on effects of cadmium on the ovaries has been generated by the investigation of more general effects of cadmium on reproduction and early development. This includes studies on the embryotoxic and teratogenic effects of cadmium, as well as research on the transplacental transfer of the metal as a prenatal exposure route. Such studies indicate that both embryotoxic and teratogenic effects occur in many mammalian species after administration of high doses via systemic injection, but much less evidence has been advanced for such effects occurring at lower-level exposures via more environmentally relevant inhalation or oral exposure routes.

Early studies on the rat documented adverse effects of cadmium administration during pregnancy, including the demonstration of placental necrosis after high dose s.c. cadmium injections (Parizek, 1964) and heightened vulnerability of maternal animals themselves in terms of s.c. injections on day 21 of pregnancy causing hemorrhagic kidney necrosis and a 40-percent death rate among dams (Parizek et al., 1968).

In another study, Chernoff (1973) injected rats with cadmium chloride (2.5 to 7.5 mg Cd/kg) on each of 4 consecutive days, starting either on day 13, 14, 15, or 16 of pregnancy, and observed (1) a dose-dependent increase in fetal deaths, (2) decreased fetal weights, and (3) an increased rate of congenital anomalies (micrognathia, cleft palate, club foot, and small lungs). In contrast, Barr (1973) reported that cadmium chloride was not teratogenic when a dose of 16 μmole Cd/kg was injected s.c. into two different rat strains on gestation day 9, 10 or 11; but teratogenicity was observed for both strains after i.p. injections of the same doses of cadmium chloride, with marked differences between the stocks occurring in fetal mortality and incidence and types of malformations.

Studies on mice have provided further evidence for cadmium-induced embryotoxicity and teratogenicity in mammalian species. In one study, Yamamura (1972) reported that i.p. injections of 5 mg/kg of cadmium sulfate ($CdSO_4$) into pregnant mice from day 6 to 14 of gestation resulted in embryo deaths and congenital anomalies such as exencephaly, cleft palate, and bone malformations. Results obtained depended on the day of injection; that is, injections on gestation day 9 caused a low incidence of embryolethality (15 percent) and day 11 injections a high incidence of fetal death (87 percent) while injections of the same dose on day 12 produced a high lethality incidence (82 percent) but a low teratogenicity rate (5 percent). This pattern of results suggests possible differential sensitivity of fetuses or dams to various cadmium-induced effects depending upon gestation stage at which exposure occurs.

Other studies on mice have yielded information on dose-response relationships, including data suggesting a "no effect" level, and additional evidence regarding genetic influences on the induction of fetal cadmium effects. For example, Ishizu et al. (1973) exposed pregnant mice on gestation day 7 to cadmium chloride via s.c. injections of doses of 0, 0.33, 0.63, 2.5, and 5 mg Cd/kg. Dose-dependent effects were observed at doses above a no-effect level of 0.33 mg/kg. This included dose-related increases in percentages of dead fetuses (9.7, 9.9, 11.9, 12.0 and 17.5 percent at the above respective doses) and increases in percentages of malformed fetuses found when sampled on day 18 of pregnancy (0, 0, 0.97, 19.5 and 59.0 percent, respectively). Consistent with findings discussed earlier, placental but not fetal concentrations of cadmium were detected, which reinforces the idea that the metal may not cross the placental barrier very well.

Evidence for genetically inherited differential susceptibility to cadmium-induced embryotoxicity has been provided by Wolkowski et al. (1974). Pregnant female mice of two different inbred strains were injected subcutaneously on different days of gestation. Mouse embryos and fetuses of one strain (NAW) were relatively resistant to death caused by maternal injections of cadmium, whereas embryos and fetuses of the other strain (C57BL) were relatively susceptible. Pierro and Haines (1976), have also reported findings confirming the relatively high susceptibility of the C57BL strain to embryotoxic effects of cadmium, and Eto et al. (1976) have shown A/Jax mice to be susceptible to increases in the incidence of cleft lip after i.p. injections of 5.9 mg/kg of $CdSO_4$ on day 10 of gestation.

The hamster is another species that has been shown to be vulnerable to cadmium-induced embryotoxicity and teratogenicity as indicated mainly by studies carried out by Ferm and coworkers. In one of their earliest studies

(Ferm and Carpenter, 1968), intravenous injections of cadmium in hamsters on day 8 of pregnancy were found to produce teratogenic effects, especially facial malformations such as cleft palate and lips. Further characterizations of teratogenic effects were carried out in subsequent studies (Mulvihill et al., 1970; Ferm, 1971; Gale and Ferm, 1973), with similar intravenous injections of $CdSO_4$ at a dose of 0.88 mg Cd/kg being used in each. Mulvihill et al. (1970), for example, presented evidence suggesting that the palatal clefts induced by cadmium in the golden hamster are likely due to mesodermal deficiencies in the palate region typified by defects in bone formation and delays in ossification. Other congenital malformations were reported by Ferm (1971) to occur in the hamster embryo, including limb defects such as amelia and phocomelia; and Gale and Ferm (1973) reported similar effects plus others following intravenous injections of 0.88 mg Cd/kg on gestation days 8 and 9, which correspond to the time of major organ differentiation in the hamster. Effects observed included malformations of the brain, eye, jaw, and tail as well as the fore and hindlimbs.

Several investigations by Ferm and coworkers have also provided information on protective effects against cadmium-induced fetal malformations. Ferm and Carpenter (1968) showed that the simultaneous injection of zinc with cadmium protects against the teratogenic effects of cadmium. In the same study, however, Ferm and Carpenter (1968) found that cobalt did not protect against cadmium-induced teratogenic effects, in contrast to the demonstration by Gabbiani et al. (1976b) of cobalt protection against the toxic effects of cadmium on sensory ganglia and testes. Subsequent research indicated that the protective effect of zinc was not simply due to that metal's influence on the transplacental transfer of cadmium (Ferm et al., 1969). Overall, these results were interpreted by Ferm (1971) as indicating that cadmium may act directly on embryonic tissue by interfering with zinc-metalloenzymes such as carbonic anhydrase or alkaline phosphatase. By anology, possible interactions of cadmium with selenium-dependent enzymes may also be indicated in view of protection being offered against teratogenic effects of cadmium by selenium administered within 30 minutes of an injection of an otherwise teratogenic dose of cadmium. Also, Semba et al. (1974) demonstrated that pretreatment with low doses of cadmium before injections of high doses of the metal protects against high-dose cadmium teratogenic effects such as exencephaly. In view of these latter results, a possible induction of a protective metallothionein protein might be hypothesized to explain the protective effects of zinc and other metals against cadmium's teratogenic effects.

It should be noted that not all heavy metals exert beneficial effects when administered with cadmium. Thus, although simultaneous injections of cadmium and inorganic lead salts in the pregnant hamster yielded protective effects against typical teratogenic effects of cadmium, such combined injections apparently potentiated characteristic teratogenic effects of lead. They also induced some effects, e.g., severe malformations of the lower extremities and umbilical hernias, not usually seen after the injection of either metal alone (Ferm and Carpenter, 1968). Similarly, additive embryotoxic effects are seen if cadmium is injected along with mercury (Gale, 1973).

The above studies utilized acute or subacute systemic injections of relatively high doses of cadmium; questions can therefore be raised about the relevance of the observed fetotoxic and teratogenic effects for the assessment of potential effects in humans typically exposed via different routes (oral and inhalation) and to much lower levels of cadmium. Of more importance for present purposes, then, are animal studies which have employed inhalation or oral exposure routes for the administration of low levels of cadmium on a more chronic basis. The papers to be considered are those by Cvetkova (1970), Schroeder and Mitchener (1971), Pound and Walker (1975), Wills et al. (1976), Choudhury et al. (1977), and Campbell and Mills (1974).

In the Cvetkova (1970) study, female rats were exposed for up to 7 mo to $CdSO_4$ (3 mg/m^3) via inhalation. Alterations in the estrous cycle were observed in 50 percent of the exposed rats by 2 mo and in 75 percent by 4 mo, before mating was carried out. Upon sacrifice of half of the pregnant dams on gestation day 22, no significant effects on fetal mortality were found, nor was evidence obtained for prenatal teratogenic effects of cadmium. The remaining control and exposed mothers delivered litters of comparable sizes, but the offspring of the exposed mothers were smaller, weighed less than those in control litters, and experienced a higher perinatal mortality rate.

Evidence for teratogenicity of orally administered cadmium was reported by Schroeder and Mitchener (1971). They exposed mice to cadmium in the drinking water at doses of 10 μg Cd/ml continuously throughout a sequence of breeding of randomly selected pairs of males and females over a 6-mo exposure period. Males and females randomly selected from among the F_1 generation litters were similarly allowed to breed ad libitum, as were pairs from the succeeding F_2 generation. Control animals not exposed to cadmium were bred in a similar manner. The results indicated that orally administered cadmium was quite toxic to breeding mice, with some congenital anomalies such as sharp angulation of the tail being seen in exposed F_1 and F_2 generation offspring as well as increased mortality before weaning and reduced rates of growth. The experiment was discontinued when 3 of 5 exposed F_2 generation pairs failed to breed.

Pond and Walker (1975) assessed the effects on reproduction of 200 ppm of Cd as $CdCl_2$ added to diets varying in calcium content (0.07 percent and 0.96 percent calcium). Although numbers of live or stillborn pups per litter were not significantly altered and no gross anomalies were seen, high cadmium content in the diet did significantly reduce pup birth weight. Concentrations of cadmium in the bodies of pups were doubled in the low-calcium groups when compared to the high-calcium dosed animals.

Wills et al. (1976) evaluated the effects of orally administered cadmium on both rats and monkeys. Both male and female rats were exposed via feed containing 33 or 73 ppb of cadmium chloride, and monogamous matings were allowed until four litters per couple were produced. Exposure at 33 or 73 ppb of cadmium via the feed continued for the offspring, which were also mated, as were successive generations until four generations had been produced. There was a slight increase in fertility among the 73 ppb exposure group animals but not in the 33 ppb group. Body-weight gain deficits were observed at both exposure levels, but no significant macroscopic or microscopic changes were found in the 286 rats assessed that could be attributed to the cadmium exposures. Rather, relatively minor changes observed were thought to be due to spontaneous disease, including tumors of similar types found in control and both cadmium-exposure groups. The lack of striking morphological changes might be expected, however, in view of the very low, almost trace amounts of cadmium used (which were below levels normally seen in most rat chows).

The same authors (Wills _et_ _al_., 1976) also fed four female monkeys cadmium chloride in a sweetened beverage at 1.5 or 3.0 μg/kg/day, with a fifth monkey serving as a nonexposed control. Unfortunately, the control monkey and one exposed at 1.5 μg/kg died after 6 months from disease processes apparently unrelated to the cadmium exposure. The other females, which survived 18 months of cadmium exposure, were mated with nonexposed males; one at each dose level became pregnant and each later delivered a single infant, the lower-dose animal prematurely. No congenital anomalies were seen, and both infants appeared to nurse and develop normally. These results do not suggest that the cadmium exposure used had any major effects. They are, however, of very limited value due to the very small numbers of animals tested.

While the results of Wills _et_ _al_. (1976) on monkeys are of very questionable import, the findings obtained in the other studies on rats and mice do appear to have some value for the analysis of the effects of chronic low-level cadmium exposures on reproduction and development. In at least one study (Schroeder and Mitchener, 1971), for example, significant teratogenic effects were found, but with the anomalies seen after long-term oral exposure being different from those reported in earlier studies to be induced by acute, high-level exposure via systemic injections. Another, much more consistent effect reported in several of the studies, however, is that of reduced birth weights and/or deficits in postnatal body weight gain for the offspring of rats or mice chronically exposed to cadmium. One crucial question, then, concerns the etiological bases underlying the observed body weight deficits, i.e., are they due to direct effects of cadmium on the fetus resulting from transplacental transfer of the metal or do such deficits occur secondarily as the result of other cadmium effects, including possible actions on mothers of affected offspring? A number of studies have generated results bearing on this issue and, in general, appear to indicate that transplacental transfer of the metal probably plays a far less important role than other factors.

Many studies indicate that transplacental transfer of cadmium does not occur to any great degree. Ishizu et al. (1973), for example, reported on pregnant mice which were given s.c. injections of 2.5 mg Cd/kg as cadmium chloride on day 7 of pregnancy. Cadmium concentrations were about 10 times higher in the placentas of the cadmium-exposed animals than in controls, but the fetal concentrations were similar in each group (about 0.03 μg/g) although the levels in the liver and placenta of exposed mothers were 17 μg/g and 0.19 μg/g, respectively.

The Ishizu et al. (1973) results are consistent with findings of little fetal uptake during late gestation as assessed by autoradiography (Berlin and Ullberg, 1963). They also comport well with other results. Specifically, Ferm et al. (1969) showed that only small amounts of radioactive cadmium reached the fetus on the eight to ninth day of gestation in the hamster, while Wolkowski (1974) found that trace amounts of ^{109}Cd crossed into the fetus on days 13 and 17 of gestation in mice and Lucis et al. (1971) reported that only low amounts of cadmium crossed the placenta during the first third of gestation in the rat.

More specific characterization of parameters associated with transplacental transfer of cadmium in animals has been attempted, both by autoradiography (Dencker, 1975) and biochemical evaluations (Sonawane et al., 1975). In the Dencker study, pregnant hamsters and mice were injected intravenously with 20 µCi $^{109}CdCl_2$ (i.e., 0.21 g ^{109}Cd) at different times during pregnancy. Then, the whole animal, the uterus, or the embryos were processed for autoradiography. On the eighth day of gestation, low amounts of cadmium accumulated in the gut of embryos of both species. None, however, was found in the embryos with injection beyond the ninth day (hamster) or the eleventh day (mouse).

In the Sonawane *et al*. (1975) study, placental transfer rates of cadmium in rats were assessed in relation to dose (0.1, 0.4 and 1.6 mg Cd/kg) and gestational age (12, 15 and 20 days) at which pregnant dams were injected intravenously with a single dose of $^{109}CdCl_2$ (approximately 20 µCi/animal). The animals were sacrificed 24 hr after injection of the tracer, and ^{109}Cd concentrations were measured in the fetus, placenta, maternal liver, and blood. As shown in Table 2-3, very small amounts of cadmium were found to cross the placenta at each dose and gestation age, with increasing amounts accumulating in the fetus as a function of increasing dose and gestational age. Also, placental to maternal blood cadmium concentration ratios increased with gestational age but not with dose (Table 2-4), and placental to fetal cadmium concentration ratios decreased in reverse relationship to increasing dose and age, as shown in Table 2-5. These results contrast with some of those described above, which suggested that early cadmium crossing of the placental barrier occurs early, but not late, in pregnancy. In either case, it appears that only a very small amount of transplacental transfer of the metal occurs in experimental animals during pregnancy.

As for transplacental transfer of cadmium in humans, only barely detectable levels have been reported to exist in human fetuses at various

Table 2-3. CADMIUM IN PLACENTAS AND FETUSES[a]

	Dose, mg/kg	Cd, %/g of injected dose[b]		
		Gestation day 12	Gestation day 15	Gestation day 20
Placentas[e]	0.1	0.063 ± 0.043 (1.6)	0.0115 ± 0.49 (5.8)	1.403 ± 0.293 (5.6)
	0.4	0.232 ± 0.032[c] (1.6)	0.142 ± 0.124[d] (4.7)	1.347 ± 0.127 (5.8)
	1.6	0.206 ± 0.057[c] (1.3)	0.466 ± 0.147[d] (3.8)	0.587 ± 0.167 (6.9)
Fetuses[f]	0.1	0.00012 ± 0.00004 (1.1)	0.0014 ± 0.0001 (6.8)	0.0019 ± 0.0003 (64.7)
	0.4	0.0022 ± 0.0023[d] (1.1)	0.0027 ± 0.001[d] (7.6)	0.0036 ± 0.0016[d] (69.1)
	1.6	0.0217 ± 0.0111[d] (0.9)	0.0096 ± 0.0026[d] (4.9)	0.0152 ± 0.0058[d] (50.8)

[a] From Sonawane *et al.*, 1975; rats sacrificed 24 hr after Cd treatment at various dose levels.

[b] Numbers in parentheses indicates average weight of placentas per litter or average fetal weight per litter. At least three animals were used to obtain each value.

[c] Significantly different from 0.1 mg/kg dose level, $p < 0.05$.

[d] Significantly different from 0.1 mg/kg dose level, $p < 0.01$.

[e] The dose-response test for placental data revealed significant dose-response relationships for day 12 and day 15 groups significant gestational day relationships at the 0.1 and 1.6 doses at least at $p < 0.05$.

[f] The dose-response test for fetal data revealed significant dose-response relationships for all gestational groups and gestational day differences at the 0.1 dose at least at $p < 0.01$.

Table 2-4. PLACENTAL TO MATERNAL BLOOD CONCENTRATION RATIOS[a]

Dose, mg/kg	Ratio placental: maternal blood Cd Gestation day 12	 Gestation day 15	 Gestation day 20
0.1	14.9 ± 3.0	37.9 ± 7.8	118.8 ± 47.7[b,c]
0.4	12.3 ± 6.4	26.8 ± 4.5	58.7 ± 17.2[b,c]
1.6	11.8 ± 7.9	25.9 ± 8.8	52.5 ± 36.3[b,c]

[a] From Sonawane et al., 1975.

[b] The dose-response test revealed significant gestational day differences for all doses at least at $p < 0.05$.

[c] Significantly different from the 12th day treatment, $p < 0.01$.

Table 2-5. PLACENTAL TO FETAL CADMIUM CONCENTRATION RATIOS[a]

Dose, mg/kg per day	Ratio placental: fetal Cd Gestation day 12	Gestation day 15	Gestation day 20
0.1[c]	618.00 ± 409.11	103.94 ± 29.28	78.877 ± 32.248
0.4	266.11 ± 232.92[b]	55.92 ± 17.41	41.852 ± 16.786[b]
1.6	11.23 ± 4.16[b]	56.64 ± 7.56	42.690 ± 2.244[b]

[a] From Sonawane *et al.*, 1974; ratios are based on percentage of injected dose/g found in placentas and fetuses.

[b] Significantly different from 0.1 mg/kg dose level, $p < 0.01$.

[c] The dose-response test revealed significant dose-response relationships for the day 12 and day 15 groups at least at $p < 0.01$.

gestation stages based on analysis of autopsy materials (Chaube, 1973). Further confirmation of this applying to humans is provided by the work of Baglan et al. (1974) demonstrating only relatively small amounts of cadmium in freshly obtained human placentas, umbilical cord blood, and fetuses.

Given that only very small amounts of cadmium cross the placenta and accumulate in the fetus based on the above data, other factors are probably crucial in mediating cadmium effects on fetal and neonatal growth and development. Among such factors implicated as likely being important are effects of cadmium on maternal and fetal levels of essential elements such as zinc and copper. Maternal zinc deficiency has been shown to cause fetal abnormalities in experimental animals (Hurley and Swenerton, 1966; Hurley et al., 1971), and it would not be surprising if well-known effects of cadmium on zinc distribution were exacerbated in pregnant animals in a manner so as to induce fetal abnormalities secondary to a maternal or fetal zinc deficiency. Consistent with this, Pond and Walker (1975) and Choudhury et al. (1977) have reported lowered zinc concentrations and decreases in birth weight in pups of rats orally exposed to cadmium during gestation either at 200 mg/kg of cadmium in the diet or at 17.4 mg/l of cadmium in the drinking water, respectively. The results of the Choudhury et al. (1977) study are summarized in Table 2-6. Interestingly, no increase in fetal cadmium accompanied decreases in fetal zinc and other elements in the Choudhury et al. study, suggesting that such effects were likely secondary to cadmium influences on maternal nutritional state rather than directly on the fetuses.

Table 2-6. EFFECT OF MATERNAL DIETARY CADMIUM (17.2 μg/ml), GIVEN DURING GESTATION, ON BODY WEIGHTS AND BODY TRACE METALS OF NEONATES[a]

Experimental group	Birth weight (g)	Lactation wt. gain (g)	Zinc	Copper	Iron	Cadmium
			(μg/g pup dry weight)			
Control	6.8 ± 0.1	52 ± 1.0	116 ± 4	9.4 ± 0.4	330 ± 6	0.46 ± 0.05
Cadmium	6.4 ± 0.1*	44 ± 1.6	104 ± 3*	5.7 ± 0.4**	267 ± 17**	0.48 ± 0.04

[a] From Choudhury, et al., 1977.

Data expressed as means ± SEM. Statistically significant difference, Student "t" test.

* $p < 0.05$.

** $p < 0.01$.

to cadmium influences on maternal nutritional state rather than directly on the fetuses.

In both the Choudhury et al. (1977) and the Pond and Walker (1975) study, fetal copper as well as zinc levels were reduced by cadmium exposure during pregnancy, and iron levels were also significantly reduced in the Choudhury et al. study. Consistent with the findings on copper reductions in fetal rats, Anke et al. (1970) have reported a trend toward reduced copper levels in newborn lambs after cadmium exposure of maternal ewes during pregnancy. Fetal concentrations of cadmium, however, were not increased, again suggesting that the fetal effects were secondary to effects on the maternal animal or cadmium inhibition of transplacental transfer of copper.

Persisting effects of cadmium exposure during pregnancy on the postnatal development and growth of offspring have also been demonstrated. For example, Choudhury et al. (1977) reported that the neonates experiencing the above types of essential element deficiencies, which were weaned without access to cadmium except that contained in the mother's milk during suckling, were later found to exhibit significantly depressed spontaneous activity and other neurobehavioral deficits in the absence of any overt teratogenic effects. Similarly, deficits in growth, plasma copper concentrations, and cytochrome oxidase activities have been reported for lambs born to ewes exposed to 3 mg/kg of cadmium in the diet (Bremner and Campbell, 1978).

2.8 ENDOCRINE EFFECTS OF CADMIUM

Only limited information exists on possible endocrine effects exerted by cadmium, with most studies bearing on this issue having employed relatively high doses of cadmium often given by injections rather than lower doses administered orally or by inhalation. Still, a variety of endocrine effects have been demonstrated, and some of the more salient findings are reviewed below.

2.8.1 Gonadal Effects

Extensive evidence documents the effects of cadmium on the gonads, especially the testes, as was reviewed in some detail under the earlier Reproduction and Development section (2.7). As reviewed there, severe testicular necrosis has been well established as being one of the more notable consequences of high-level cadmium exposure, and that necrosis has been shown to involve endocrine cells within the testes as well as the testicular vasculature and germinal epithelium. In fact, some evidence was cited which suggests that damage to the endocrine (Leydig) cells of the testes may occur at cadmium-exposure levels below those producing initial signs of significant kidney damage (i.e., proteinuria). At high dose levels, consequently altered testosterone productions may contribute to deterioration of testicular germinal epithelium and other androgen-dependent tissues. In contrast, as also reviewed earlier, relatively little evidence has been advanced for cadmium effects on female gonads.

2.8.2 Pancreatic Effects

High accumulation of cadmium in the pancreas of humans and animals has been reported in several studies of cadmium poisoning (Friberg, 1957; Smith et al., 1960; Barbieri et al., 1961; Ishizaki et al., 1970; Nordberg and Nishiyama, 1972), as has altered pancreatic excretory function in Itai-Itai patients (Murata et al., 1970). This suggests that the metal may affect the pancreas, and cadmium effects on carbohydrate metabolism have been hypothesized as being due to cadmium-induced damage to the pancreas.

In regard to the induction of hyperglycemia by cadmium, reported to occur in rabbits (Voinar, 1962), dogs (Caujolle et al., 1964) and mice (Ghafghazi and Mennear, 1973), evidence has been advanced for that effect being mediated mainly through the adrenals rather than the pancreas (Ghafghazi and Mennear, 1973). Reductions in glucose tolerance induced by cadmium, however, have been linked to cadmium-induced alterations in pancreatic function. Evidence supporting the possibility of cadmium-induced effects on pancreatic secretory activity include: (1) the finding that cadmium accumulated equally in endocrine and exocrine parts of the pancreas (Friberg and Odeblad, 1957), and (2) the demonstration of decreases in the ratio of pancreatic beta to alpha cells in the rabbit after cadmium treatment (Barbieri et al., 1961), and (3) reports of observed decreases in concentrations of circulating insulin in mice after a single cadmium injection (Ghafghazi and Mennear, 1973). In addition, Ithakissios et al. (1975) treated rats every other day for 70 days by injections of cadmium acetate solution at 0.25 to 0.50 mg Cd/kg i.p. and found decreased insulin secretion at the 0.50 mg/kg dose.

That glucose tolerance may be impaired through cadmium reducing the insulin secretion of the pancreas, has been implicated more directly through the demonstration of Ghafghazi and Mennear (1975) of cadmium inhibition of insulin secretion by the isolated perfused rat pancreas in response to glucose challenge. The latter authors hypothesize that the effect is most likely due to interference by cadmium with calcium uptake by the pancreatic beta cell.

Possible protective effects of various substances against the pancreotoxic effects of cadmium have also been investigated. For example, Merali and Singhal (1975) reported that administration of selenium concurrently with cadmium ameliorated cadmium-induced hyperglycemia, hypoinsulinemia, glucose intolerance, and suppression of pancreatic secretory activity. Also, Ghafghazi and Mennear (1973) found that repeated administrations of cadmium did not produce the significant reduction in pancreatic insulin secretion seen after a single larger injection of the metal, and Yau and Mennear (1973) obtained results suggesting that a pancreatic metallothienin protein is produced in response to cadmium.

2.8.3 Adrenal Effects

The possible involvement of the adrenals in the mediation of cadmium effects on other organ systems has been suggested by several studies. For example, Ray and Chatterjee (1973) found that reserpine and adrenalectomy blocked certain cadmium-induced effects on the testicles, and they hypothesized that adrenal catecholamines (CA's) may be important in mediating cadmium effects on the testes, perhaps by affecting testicular blood flow. Also, evidence has been advanced for the induction of hyperglycemia by cadmium being mediated through effects on the adrenals, since adrenalectomy abolished the hyperglycemic response of mice to cadmium (Ghafghazi and Mennear, 1973).

More direct evidence for cadmium affecting the adrenals has been generated. For example, Hart and Borowitz (1974) demonstrated that cadmium was moderately effective in causing prolonged release of CA *in vitro*, possibly through interactions with intracellular calcium in adrenal medullary cells. In a follow-up study, Leslie and Borowitz (1975) obtained data interpreted as indicating that not only can cadmium initiate catecholamine secretion from the adrenal medulla, but it also appears to interfere with calcium removal from adrenal medullary cells, thereby inhibiting termination of the secretory response.

Additional data consistent with the above have been obtained in an *in vivo* study by Rastogi and Singhal (1975). Adolescent male rats were injected i.p. daily with cadmium chloride at doses of 0, 0.25, or 1.0 mg/kg for either 21 or 45 days. The results showed that daily treatment with either 0.25 or 1.0 mg/kg of cadmium for 21 days significantly increased adrenal weights, but such weights were still increased after 45 days of exposure only in the 1.0 mg/kg group. On the other hand, treatment at either dose level resulted not only in significantly enhanced CA levels after 21 days but also in even more marked increases in CA levels by 45 days and significant increases in tyrosine hydroxylase (TH) activity in the 1.0 mg/kg group after 45 days. Discontinuation of cadmium exposure for 28 days failed to restore normal adrenal weights in the 1.0 mg/kg animals, but CA levels returned to control values, as did TH activity. These results suggest that cadmium exerts significant, although apparently reversible effects, on adrenal medullary CA synthesis at i.p. dose levels as low as 0.25 mg/kg.

Adrenal cortical functions, as well as adrenal medullary secretions, appear to be affected by cadmium, according to a study by Der et al. (1977a), which compared the effects of cadmium and lead on thyroid and adrenal functions. Adult male rats weighing 300 g received daily intramuscular (i.m.) injections of 50 or 250 µg of cadmium chloride, while other rats received either 50 or 250 µg of lead or simultaneous injections of 25 µg each of lead acetate and cadmium chloride. Significant deficits in weight gain and increased adrenal weights were observed during 70 days of cadmium exposure at the 250 μg dose. Also, adrenal histology evaluations revealed increased nuclear diameters in cells of the zona glomerulosa and fasciculata of both the 50- and 250-μg cadmium-dose groups; and plasma corticosterone levels were found to be significantly elevated in the 50- and 250-μg cadmium groups and the combined 25-μg lead-cadmium group. These results provide evidence for adrenal cortical hypertrophy after chronic cadmium treatment, resulting in increased adrenal corticosteroid secretion. It remains to be seen, however, as to whether such effects occur after exposure to cadmium via oral ingestion or inhalation.

2.8.4 Thyroid Effects

The demonstration of high thyroid cadmium levels in human autopsy material (Friberg, 1957), as for the pancreas, raises the possibility of the thyroid being a target organ for the metal. Relatively sparse information, however, exists concerning cadmium effects on the thyroid. In the Der _et_ _al_. (1977a) study mentioned earlier, evidence was found for significant decreases being induced in plasma T_4 levels in rats by the 250 μg cadmium chloride treatment and in plasma T_3 levels by the 50 μg and 250μg cadmium doses as well as by the combined 25 μg lead and cadmium treatment. No evident changes in thyroid histology accompanied the decreases in thyroid hormone secretion seen with any of the treatments. Nevertheless, Der _et_ _al_. (1977a) hypothesized that the hypothyroid state induced by cadmium might be responsible for a decreased rate of body weight gain observed for the 250 μg cadmium dose group and might also contribute to increased susceptibility to various disease resulting from cadmium-induced immune suppression effects.

2.8.5 Pituitary Effects

An important point to consider in the interpretation of the above endocrine effect studies is the difficulty that exists in disentangling possible direct effects of cadmium on the endocrine organs discussed from effects that may be exerted via cadmium actions on the pituitary and vice versa. At least a few examples have been cited in regard to changes in the pituitary itself after cadmium exposure. One such effect is the decrease in pituitary weight reported by Der et al. (1977a) after exposure of female rats to 250 μg cadmium chloride for 54 days.

Other pituitary effects seen after cadmium include hyperplasia of gonadotropic cells and increased numbers of prolactin secreting cells in the anterior pituitary of male rats as revealed by immunofluorescence methods (Girod and Dubois, 1974, 1976). Consistent with this observation is the reported increase in plasma leuteinizing hormone (LH) level (Chandler et al., 1976) seen in cadmium-exposed rats for which ultrastructural evidence was obtained for changes in the entire interstitial-tubular complex of the male reproductive tract. Whether the observed pituitary cytology changes and LH increases represent a direct effect of cadmium on the pituitary or occur secondarily to damage to the testes by the metal presently is not clear. The possibility remains that at least some endocrine-related effects associated with cadmium exposure may be exerted via cadmium effects on the pituitary directly, and this possibility is reinforced by the Berlin and Ullberg (1963) finding of some accumulations of cadmium in that gland.

2.9 EFFECTS OF CADMIUM ON BONE AND MINERAL METABOLISM

The effects of cadmium on bone arises from chronic exposure, and this derangement appears to be secondary to renal malfunction through disturbance in calcium and phosphorus metabolism. The literature detailing the effects of cadmium on calcium metabolism and bone structure in experimental animals suggests that this may indeed be the case.

2.9.1 Animal Studies

In the studies of Kawai *et al*. (1974), in which rats were chronically dosed with cadmium (10 to 200 μg Cd/ml in drinking water, up to 8 1/2 mo), histological findings in the bone appeared in the 50 ppm Cd group, and higher exposure levels were associated with decalcification and cortical atrophy of the femur. Calcium content also was reduced in the highest level (200 (μg/ml) exposure group.

The data of Itokawa *et al*. (1974) demonstrated effects of cadmium on bone in rats using an exposure level of 50 ppm in water and either calcium-adequate or calcium-deficient diets. In both of the cadmium-treated groups, urinary calcium and phosphorus levels were significantly reduced, with thinning of the cortical osseous tissue seen in bones of cadmium-exposed animals which were fed a calcium-deficient diet. Furthermore, fat deposition occurred in the femoral spongiosa in both cadmium groups, while the cadmium-exposed animals on the low-calcium diet manifested osteoid borders on trabeculae and an increased number of osteocytes. These authors pointed out the similarity of this osteopathology with the osteomalacia seen in man. This osteopathology may be secondary to early renal glomerular damage occurring before the onset of tubular dysfunction.

Abe *et al*. (1972) gave rats cadmium in diet corresponding to a daily ingestion of 1.5 mg and observed after 4 wk that this dosing regimen, along with diets low in protein and calcium, led to abnormal curvature of the spine.

Reference was made in the section on renal effects (2.5) to the inhibitory action of cadmium on the conversion of 25-hydroxy-Vitamin-D_3 to the physiologically active essential metabolite, 1,25-hydroxy-Vitamin-D_3. Sugawara and Sugawara (1974) observed decreased calcium absorption in rats receiving 50 ppm cadmium in drinking water. Also, in a recent report, Kawai (1976) noted decalcification and cortical atrophy in bone tissue with chronic dietary exposure to cadmium.

2.9.2 Human Aspects

In man, osteomalacia and severe osteoporosis are known effects of chronic cadmium exposure, in both occupational settings and in populations sustaining pronounced cadmium exposure (Nordberg, 1976; Friberg et al., 1974).

As noted elsewhere, Itai-Itai disease is a patho-physiological triad of renal tubular dysfunction, osteoporosis, and osteomalacia. There appears to be no question that there is a nutritional component to the manifestation of the disease: calcium and Vitamin-D deficiency in postmenopausal women with a history of multiple childbirth and past probable deficiency in these two factors. Osteopathic symptomatology (Friberg et al. 1974) of the disorder includes: Milkman's pseudo-fractures and fractures, thinned bone cortex, decalcification, deformation, fishbone vertebrae, and coxa vara. Biochemical changes include decreased serum P_i and a decreased urinary P/Ca ratio.

2.10 HEPATIC EFFECTS OF CADMIUM

Although hepatic tissue is one of the sites where cadmium accumulates and induces functional alteration, the literature is not so extensive as that which exists for renal, pulmonary, and cardiovascular effects. Liver is the major biosynthetic organ for metallothionein in a number of experimental animal species and man, so any consideration of the extent of hepatic functional derangements as a function of the amount of cadmium present in liver must take this factor into account.

2.10.1 Animal Studies

It was noted earlier that cadmium, at high doses, has an effect on the drug-detoxifying actions of enzyme complexes, as measured by several techniques, including sleeping-time changes and enzyme inhibition.

Further animal studies have been carried out on the hepatic effects of cadmium under varying experimental conditions. For example, Andreuzzi and Odescalchi (1958) found that rabbit serum glutamic-oxaloacetic-transaminase was elevated following intravenous administration of cadmium (1.25 to 3.0 mg/kg, 24 to 72 hr), with a ten-fold or greater increase after 24 hr using the largest dosage, which killed 60 percent of the animals within 24 hr. These workers concluded that a dose approaching the LD_{50} was required to produce severe liver lesions, while lower exposure effects were reversible.

Neige *et al*. (1974) showed that rats given 4 subcutaneous injections per week of cadmium sulfate (3 mg Cd/wk) displayed, after 60 days, cytoplasmic necrosis of hepatocytes, festooning of nuclear membranes, and round intra-nuclear inclusions.

Colucci *et al*. (1975) induced pathological changes in rat hepatic tissue by the i.p. injection of cadmium (0.5 to 4.0 mg/kg, t to 6 days). Animals in the 0.5 and 1.0 mg Cd/kg groups showed no microscopic hepatic abnormalities. Those in the higher dose groups revealed degenerating hepatocytes. These workers found that, when liver cadmium levels were below 30 μg Cd/g wet weight, the metal was sequestered as metallothionein, and no apparent toxicity was evident. Levels of 40 μg Cd/g were associated with hepatic cellular degeneration as well as other systemic pathology.

Faeder et al. (1977) investigated biochemical ultrastructural changes in hepatic tissue of rats exposed to cadmium at levels known to induce hepatic changes but administered so as to minimize clinical signs of morbidity (subcutaneous injection, 0.25 to 0.75 mg Cd/kg, 3 times/wk for 8 wk). After 6 wk, animals given 0.5 mg/kg showed dilation and loss of ribosomes from the endoplasmic reticulum, with the additional feature of swollen mitochondria observed at the 0.75 mg/kg dose level. Biochemically, plasma aspartate aminotransferase (AAI), a-glutamyl transpeptidase, and erythrocyte carbonic anhydrase activities were elevated by the sixth week of exposure.

Sequential changes in hepatic polyamine, DNA, and cyclic AMP metabolism were reported by Kacew et al. (1977) in rats subacutely exposed to cadmium (1 mg/kg, twice a day for 3, 5 and 7 days). Hepatic levels of spermidine and spermine were significantly lowered while hepatic DNA synthesis was increased. Stimulation of the hepatic adenylate cyclase-cyclic AMP system was noted to occur as early as 1 day.

It should be noted that morphological changes in the liver occur before changes in hepatic marker enzymes activities.

2.10.2 Human Aspects

While an acute effect of cadmium on liver function in occupationally exposed men has been seen, liver disturbances are not a common finding in the human toxicity of cadmium; and gross changes are quite rare (Friberg et al., 1974).

2.11 NEUROLOGICAL EFFECTS OF CADMIUM

Perhaps not surprising in view of the relatively low uptake of cadmium into brain and other neural tissue, potential neurological effects of cadmium have been accorded much less attention in the research literature than many other types of cadmium effects. Only a few studies of humans occupationally exposed to cadmium have provided any evidence for cadmium-induced neurological damage, and that has been largely confined to apparent deficits in sensory functions. Also, comparatively little convincing evidence for neural effects has been demonstrated by the limited number of animals studies that have been conducted.

In regard to human studies, Friberg (1950) reported that 37 percent of 43 cadmium-exposed workers studied had olfactory impairments. Those workers, however, were also exposed to nickel dust. Adams and Crabtree (1961), too, found evidence for hyposmia and anosmia when they compared a group of 106 battery workers exposed to cadmium oxide and nickel dust to 84 age-matched, non-exposed control subjects. Significantly more battery workers reported themselves to have olfactory problems than control subjects (15 vs 0 percent, respectively), and they did less well than controls on a phenol-smelling test. Anosmia correlated well with proteinuria, with 17 battery workers exhibiting proteinuria also being anosmic. Signs of local nasal irritation, ulceration, and dry crusting suggested likely direct damage to the olfactory mucosae. Olfactory impairment in the same worker population was also found by Potts (1965) in 53 to 65 percent of the battery-factory workers exposed 10 to 29 years to cadmium oxide dust and in 91 percent exposed for over 30 years; again, the workers were likely exposed to nickel as well as cadmium. Tsuji et al. (1972), on the other hand, reported impaired olfaction in workers exposed to cadmium at a zinc refinery, where no concomitant nickel exposures were encountered. While these results suggest that cadmium may cause direct damage to nasal olfactory mucosae, it should be noted that such effects apparently only occur at extremely high inhalation exposure levels that were previously of concern in industrial situations; and little evidence for such effects at lower exposure levels has yet been provided by animal or human studies.

About the only other report of signs of possible cadmium-induced neural damage in humans is that of Vorob'yeva (1957) on changes in the "chronaxies" of cutaneous sensory and optic nerves of cadmium-exposed workers, but, again, little confirmation of any peripheral nerve damage has come from other human or animal studies.

What little evidence from animal studies that exists for cadmium effects on neural tissue comes mainly from *in vitro* work. This includes reports that cadmium chloride exerts toxic effects on gasserian and spinal sensory ganglia (Gabbiani *et al*., 1967a; Schlaepfer, 1971), cerebellar tissue (Kasuya *et al*., 1974), and other central nervous system (CNS) tissue (Gabbiani *et al*., 1967b). Pathological changes observed by Kasuya *et al*. (1974) included inhibition by cadmium stearate of normal outgrowth of cerebellar cells cultured from brains of newborn rats. Still other effects of cadmium on neural functions have been demonstrated *in vitro*. Edstrom and Mattson (1976), for example, studied the effects of sulfhydryl blocking agents on the *in vitro* rapid axonal transport of ^{3}H-leucine-labelled proteins in the frog sciatic nerve. Rapid transport of the proteins was inhibited in the presence of low concentrations of divalent heavy metals including cadmium.

Research in other studies has focused on possible molecular mechanisms by which cadmium might affect neurotransmission, with some consistent results emerging from such studies. In one study, Kamino et al. (1975) utilized synaptosomes isolated from rat brain cortex to investigate the effects of cations on synaptosomal CA^{++}-binding. Cadmium, as well as other cations tested, significantly inhibited synaptosomal Ca^{++}-binding, suggesting possible disruptive effects on presynaptic transmitter release or uptake mechanisms.

Consistent with the above interpretation, several studies have demonstrated cadmium effects on neurotransmission, including effects on release of particular transmitters. In that regard, Chen (1975) studied the effects of divalent cations and catecholamines on the "late response" of the superior cervical ganglion of dogs and found that catecholamines suppress that response, while certain divalent ions such as cadmium potentiate and prolong it. Chen (1975) concluded that cadmium chloride may inhibit sympathetic ganglionic transmission by presynaptic suppression of acetylcholine release. Similar conclusions were reached by Toda (1976) and Forshaw (1977), who presented evidence for inhibitory effects of cadmium on neuromuscular transmission in isolated frog striate muscle and isolated rat diaphragm, respectively. Toda (1976) concluded from his overall data that cadmium interferes with the release of acetylcholine from motor nerve terminals by reducing the transmembranous influx of calcium, and Forshaw (1977) concluded that cadmium reduced the quantal release of transmitter in the isolated phrenic diaphragm by inhibition of calcium function at presynaptic nerve terminals. Cooper and Steinberg (1977) reported results they interpreted as indicating that cadmium blocked adrenergic neuromuscular transmission in the rabbit primarily through an effect on presynaptic nerve terminals.

Ribas-Ozonas et al. (1974) reported decreases in regional brain serotonin (5-hydroxytryptamine, 5-HT) levels after intraventricular injection of a 33 μg dose of cadmium chloride 1 to 3 days before the injected rats were sacrificed. Subsequently, Hrdina et al. (1976) studied the effects of chronic (45 days) i.p. injections of doses of cadmium chloride (0.25 and 1.0 mg/kg/day) on the regional levels of brain neurotransmitters and associated enzymes. Both doses of cadmium produced significant decreases in cortical acetylcholine and brainstem 5-HT and a transient increase in striatal dopamine. Cadmium-induced decreases in brain 5-HT levels persisted even after withdrawal of cadmium treatment for 28 days before sacrifice. Hrdina et al. (1976) suggested that alterations in brain amine levels seen after cadmium treatment may represent early signs of adverse effects on CNS function, but caution must be exercised before accepting such a conclusion. For example, the relevance for present purposes of injections of relatively high amounts of cadmium directly in the cerebroventricular system is highly questionable in view of data showing that only very low amounts of cadmium accumulate in brain tissue after systemic administration. Also, in view of cadmium's poor entry into brain, the changes in brain neurotransmitters seen by Hrdina et al. (1976) after chronic i.p. injections might be more appropriately attributed to secondary effects (possibly differential overall stress associated with cadmium exposure) rather than to direct effects of the metal on brain tissue.

Very few studies have been reported that attempt to relate cadmium exposures to neurotoxic effects manifested in terms of learning or other behavioral deficits. For example, in the Krasovskii et al. (1976) study reviewed earlier in the section on reproduction and development, it was claimed that "changes" in the conditioned reflex activity of experimental animals" were seen with oral exposures to 0.005 and 0.0005 mg/kg doses of cadmium chloride. In another study (Pihl and Parkes, 1977) hair samples from 31 learning disabled and 22 normal children were analyzed for content of 14 elements, including cadmium and lead; and significantly higher levels of cadmium and several other metals were reported to be found in the hair of the learning-disabled group. Given the widely recognized difficulties with hair cadmium determinations, however, these results require further confirmation.

2.12 GASTROINTESTINAL EFFECTS OF CADMIUM

Acute gastrointestinal effects of cadmium are quite uncommon in man, chiefly because the occurrence of acute cadmium poisoning by ingestion in man is rare. Chronic gastrointestinal effects of cadmium have only been seen in victims of Itai-Itai disease (Friberg et al., 1974).

In animals, studies do exist regarding the gastroenterological toxicity of cadmium. For example, shortening and thickening of mucosal villi in the duodenum of Japanese quail are seen when cadmium exposure occurs through the diet (Richardson et al., 1974) at comparatively high levels. In addition, marked hyperplasia of duodenal goblet cells occurs after 4 wk.

In a second study using Japanese quail (Richardson and Fox, 1974) cadmium fed to the birds at a level of 75 mg/kg diet from hatching to 1 mo of age led to gross, microscopic, and ultrastructural lesions in the proximal small intestines. For example, the small intestines were dilated and thin-walled, hypertrophy and hyperplasia of goblet cells occurred, microvilli of both absorptive and goblet cells were markedly shortened, and absorptive cells were atrophic and mitochondria were dense and small. Interestingly, these lesions resemble the pathological picture seen in human malabsorption syndromes, tropical and nontropical sprue, and celiac disease.

Valberg et al. (1977) assessed the relative sensitivity of mouse intestinal mucosa to cadmium-thionein and inorganic salt (cadmium chloride). Using open-ended duodenal perfusion, equivalent amounts of cadmium in either form entered the mucosa. Free cadmium ion occasioned minor derangement in the form of villi broadening and mitochondrial swelling while the protein-bound cadmium resulted in considerable damage to absorptive cells. These effects are contrasted to the observation that little bound cadmium entered the body compared with the inorganic form.

This provides further evidence (see: Renal Effects and Hepatic Effects sections) that cadmium-thionein plays a two-fold role in cadmium toxicity, i.e., on-site protection is afforded in some organs such as liver and intestinal tract while release of the cadmium-thionein from these same organs to extracellular fluid presents cadmium in a form that is functionally more toxic than the inorganic form on an equivalent metal-content basis (Cherian et al. 1977).

2.13 HEMATOLOGICAL EFFECTS OF CADMIUM

Unlike lead, where a number of hematological effects are seen over a range of that toxic element's exposure levels, comparatively less is known of the effects of cadmium on the hematopoietic system of man and experimental animals. Hematological effects appearing in the earlier literature have been reviewed (Friberg et al., 1974); Fulkerson and Goeller, 1973; Nordberg, 1974).

Cadmium-induced anemia has been observed in man from industrial exposure and in animals. The anemia is moderate, is claimed to have hemolytic and iron-deficiency components (Nordberg, 1976), and in animals appears rather early in cadmium exposure.

Prigge et al. (1977) studied the effects of dietary and inhalation cadmium on hemoglobin and hematocrit in rats as a way of assessing whether the anemia induced is related to impaired iron absorption or erythrocyte destruction. It appears that erythrocyte destruction is not a major factor in rats, since the cadmium aerosol treatment failed to elicit any anemia. In the dietary-cadmium groups (25, 50, and 100 ppm Cd in drinking water), there was a significant reduction in hematocrit and hemoglobin values, in accord with the observations of others (Fox et al., 1971; Maji and Yoshida, 1974; Freeland and Cousins, 1973).

It has also been observed that dietary iron supplement (Fox et al., 1971; Maji and Yoshida, 1974) or injected iron (Pond and Walker, 1972) restores the levels of hemoglobin and the hematocrit to normal.

The effect of cadmium on erythrocyte δ-aminolevulinic acid dehydratase (δ-ALA-D) has been studied in several animal species. Seth et al. (1976) saw no effect on δ-ALA-D) activity when mice were given cadmium by i.p. injection (2 mg Cd/kg, with and without co-injection of lead). Lynch et al. (1976), however, induced significant inhibition of δ-ALA-D activity when calves were given cadmium alone or with lead (15 mg Cd/kg body weight) contained in gelatin capsules.

Roels *et al*. (1975) could not find any relationship between cadmium and erythrocyte δ-ALA-D activity in a group of 84 workers in a cadmium works. In this case, erythrocyte metallothionein probably provided a protective function.

2.14 IMMUNOSUPPRESSIVE EFFECTS OF CADMIUM

Heightened susceptibility to the toxic effects of infectious agents has been demonstrated with cadmium exposure via several different routes, including systemic injections and oral administration of the metal. In a study by Cook *et al*. (1975b), the relative potency of lead and cadmium were compared in regard to the potentiation of an endotoxin. Neither lead acetate injected into rats intravenously at a dose of 2.25 μmol/100 g nor minute quantities of *S. enteritidis* endotoxin alone were lethal, whereas a single intravenous dose of cadmium acetate at 2.25 μmol/100 g produced a mortality of 5 percent. Simultaneous injection of cadmium acetate with the endotoxin potentiated the otherwise mild effects of the toxin much more than did lead, with 94 percent mortality being induced by cadmium and only 31 percent by lead. Also, when different doses of endotoxin were injected with the same dose of cadmium or alone, it was found that a dose of endotoxin as low as 0.12 μg/100 g produced 40 percent mortality when injected along with cadmium but a 12,500-times higher dose of the toxin was necessary to produce equivalent mortality when injected alone. By injecting the endotoxin before, with, or after cadmium, it was found that the greatest synergism occurred when the endotoxin was injected together with cadmium (94 percent mortality) rather than either 4 to 8 hr before (0 percent mortality) or after (10 to 50 percent mortality). Cook *et al*. (1975b) discuss possible mechanisms by which cadmium might exert its endotoxin-potentiating effects and report ultrastructural evidence implicating liver damage as one important factor.

In another series of studies, Koller and coworkers have also recently reported some evidence for immunosuppressive effects of cadmium administered via oral exposure. Koller (1973) reported that rabbits exposed 70 days to mercuric chloride, cadmium chloride, or lead acetate in drinking water (at doses of 10, 300, or 2,500 ppm, respectively) had significantly lower neutralizing antibody titers after inoculation with a pseudorabies virus.

Evidence for cadmium-induced increased susceptibility to disease in mice was also serendipitously observed in a subsequent study to Exon _et al_. (1975). Cadmium-stressed mice being used in the study for other purposes began dying from an intestinal infection later identified as due to _Hexamita muris_. Mice that had been exposed for 4 to 5 wk to 3 or 300 ppm of cadmium as cadmium chloride in the drinking water experienced 7 percent and 26 percent mortality, respectively. No deaths occurred, however, in non-exposed control animals. Interestingly, no "typical" cadmium lesions were found in any organs of cadmium-exposed animals, suggesting that immunosuppressive effects may be induced at substantially lower exposure levels than those required to induce other, classically defined cadmium effects.

More direct evidence for immunosuppressive effects in mice was reported by Koller _et al_. (1975). Mice exposed orally to "subclinical" doses, i.e., 3 or 300 ppm, of cadmium chloride in drinking water for 70 days experienced marked decreases in antibody-forming spleen cells, especially IgG cells, which persisted in the 300 ppm dose rats for at least six weeks after cessation of cadmium exposure. Such results suggest that immunosuppressive effects of cadmium, including that absorbed via chronic oral ingestion, may persist for quite some time after the cessation of high-level exposures.

Speculation concerning the mechanisms by which cadmium exerts its immunosuppressive effects include possible interactions with the infectious agent itself or damaging effects on various immune system cellular components. In regard to the latter possibility, Koller and Roan (1977) assessed whether mouse peritoneal macrophages were damaged by cadmium. Cadmium chloride was given orally for 10 wk at doses of 3, 30, or 300 ppm in drinking water, and the functional integrity of peritoneal macrophages was assessed. Since phagocytotic activity and acid phosphatase levels were increased in the macrophages, it was concluded that the metal activates macrophages. Based on this, it appears unlikely that immunosuppressive effects of cadmium are exerted through damage to macrophages. On the other hand, Waters *et al*. (1975) reported evidence for cytotoxic effects of cadmium on rabbit alveolar macrophages assessed in an *in vitro* model system.

In summary, it appears that cadmium does exert immunosuppressive effects both *in vitro* and *in vivo*. Furthermore, the metal appears to be many times more potent than other immunosuppressive heavy metals in potentiating certain toxic effects of various infectious agents. Lastly, the immunosuppressive action of cadmium seems, at times, to persist beyond cessation of oral exposure. Effects such as these, however, still remain to be demonstrated with human cadmium exposure.

2.15 MUTAGENIC AND CARCINOGENIC EFFECTS OF CADMIUM

Considerable concern has been generated by reports of association of cadmium exposure with mutagenesis or carcinogenesis in animals or humans. Several relevant reviews have recently appeared which deal with mutagenic effects of cadmium, the experimental induction of tumors in animals, or human cancer epidemiology studies (Flick *et al*., 1971; IARC, 1976; NIOSH, 1976; Sunderman, 1977; Carcinogen Assessment Group, 1978). As reviewed in these reports, much information has emerged in regard to the conditions under which mutagenic or tumorigenic effects can be generated experimentally in animals, whereas far less data are currently available regarding the carcinogenic potential of cadmium in humans. Still, as noted below, similar conclusions have been drawn as a result of most of the relevant reviews; that is, the assessments have typically led to the conclusion that presumptive evidence exists for cadmium-induced mutagenic and carcinogenic effects.

2.15.1 Mutagenic Effects of Cadmium

Numerous studies have focused on assessment of the mutagenic properties of cadmium; however, the evidence obtained for cadmium-induced mutagenicity in various test systems must be considered inconclusive at this time. The results of many of the more salient studies are summarized in Table 2-7.

As indicated in Table 2-7, evidence for cadmium-induced mutagenic effects has been obtained *in vitro* with several different test systems. Such evidence includes, for example, the demonstration of: (1) statistically significant increases in mispaired nucleotides when cadmium chloride was added to an *in vitro* DNA synthesis system (Sirover and Loeb, 1976); (2) abnormal mitotic and meiotic recombinations in the yeast, *Sacharomyces cerevisiae*, upon exposure to cadmium chloride (Takahashi, 1972); (3) production by cadmium chloride, but not cadmium nitrate, of mutant recombinants in strains of *Bacillus subtilis* (Nishioka, 1975) (4) unscheduled DNA synthesis in Chinese hamster embryo cells following exposure to cadmium chloride and cadmium acetate (Costa *et al.*, 1976); and (5) the induction by cadmium sulfide of chromosomal aberrations in cultured human leukocytes

Table 2-7. SUMMARY OF MUTAGENICITY TEST RESULTS

Test system	Genetic effect	Reported mutagenicity	References
	Systems in vitro		
Human cells	Chromosomal damage	+	Shiraishi et al. (1972)
Chinese hamster cells	Point mutation	+	Costa et al. (1976)
S. cerevisiae	Point mutation	+	Takahoshi (1972)
B. subtilis-recombinant assay	Gene mutation	+	Nishioka (1975)
Polynucleotides	Base mispairing	+	Sirover and Loeb (1976)
	Systems in vivo		
Human leukocytes	Chromosomal damage	+	Shirashi and Yoshida (1976)
Human leukocytes	Chromosomal damage	-	Bui et al. (1975)
Human leukocytes	Chromosomal damage	+	Deknudt and Leonard (1975)
Human leukocytes	Chromosomal damage	+	Bauchinger et al. (1976)
Mouse oocytes	Cytogenetic damage	+	Shimada et al. (1976)
Mouse breeding	Dominant lethal mutations	-	Epstein et al. (1972)
Mouse breeding	Dominant lethal mutations	-	Gilliavod and Leonard (1975)
Mouse breeding	Dominant lethal mutations	-	Suter (1975)
Mammals	Chromosomal abnormalities	-	Shimada et al. (1976)
D. melanogaster	Sex-linked recessive lethal	-	Sorsa and Pfeifer (1973)

(Shiraishi et al., 1972). Specific types of human chromosomal aberrations seen in the latter in vitro study, it should be noted, were similar to those reported for human leukocytes obtained from Itai-Itai disease patients (Shiraishi and Yoshida, 1972). Thus, in summary, mutagenic effects on genetic material or cells from a variety of species, ranging from yeast and bacteria to hamsters and humans, have been demonstrated to occur in vitro with exposure to several different cadmium compounds. The latter effects appear to be analogous to in vivo effects observed in certain human, high-level cadmium exposure cases. When considering the in vitro cadmium mutagenicity data, however, it must be remembered that, in the human or other mammalian organisms, cadmium is mainly bound to metallothionein and other proteins, and there is little evidence for ionic cadmium being present in substantial amounts.

Also as indicated in Table 2-7, several studies have yielded evidence of in vivo mutagenic effects of cadmium at high exposure levels. This includes the demonstration of (1) numerical chromosomal anomalies in mouse oocytes and blocked development of metaphase I chromosomes following injection of an acute dose of 3 or 6 mg/kg of cadmium chloride (Shimada et al., 1976); and (2) chromosomal damage in human leukocytes obtained from Itai-Itai patients (Shiraishi and Yoshida, 1972) or workers exposed to cadmium and lead (Deknudt and Leonard, 1975; Bauchinger et al., 1976).

In regard to in vivo studies finding no mutagenic effects, the one test yielding consistently negative results is that for dominant lethal mutations. In one study (Epstein et al., 1972), for example, cadmium chloride was among 174 compounds evaluated for ability to induce dominant lethal mutations in mice, but no significant evidence was obtained for the cadmium compound having such mutagenic activity at i.p. doses ranging from 1.35 to 1.70 mg/kg. Nor was any evidence for such cadmium-induced mutagenicity in mice obtained in a similar study by Gilliavod and Leonard (1975), using i.p. injections of 0.5, 1.75, or 3.0 mg/kg of cadmium chloride, or in a study by Suter (1975), in which cadmium chloride (2 mg/kg, i.p.) had no detectable dominant-lethal effects in female mice.

The results of some of the above negative studies and certain others listed in Table 2-7 have been criticized (Troast, 1978) as not being sufficiently sensitive to mutagenicity for an accurate evaluation (Gilliavod and Leonard, 1975; Sorsa and Pfeifer, 1973) or for lacking sufficient sample numbers (Bui _et_ _al_., 1975). Also, the results of Deknudt and Leonard (1975) and Bauchinger et al. (1976) may in part be due to lead as well as cadmium, since the human subjects in each of the two studies experienced exposure to both metals. Overall, the studies reviewed here and in Table 2-8 mainly provide evidence for cadmium-induced mutagenicity at high concentrations and especially with _in vitro_ test systems. Little or no data exists for mutagenic effects occurring with oral or inhalation exposure of man or other mammalian species. The significance of _in vitro_ mutagenic effects beyond their immediate implications for disruption of genetic processes in artificial testing systems therefore remains to be seen. In fact, while mutagenic properties of some compounds may correlate with their carcinogenic potential, this does not appear to hold very well in the case of cadmium or other heavy metals. Therefore, _in vitro_ mutagenetic effects of cadmium do not necessarily imply that the element is also carcinogenic.

2.15.2 Tumorigenic Cadmium Effects in Animals

Numerous studies have demonstrated the induction of tumors at sites of subcutaneous or intramuscular injections of cadmium. In that regard, Sunderman (1977) reviewed data showing that parenteral injections of cadmium powder or cadmium sulfide, oxide, sulfate, or chloride in rodents induced sarcomas at the site of injection, as also reported in a number of studies summarized in Table 2-8 (which is modified from one presented by Sunderman, 1977). In addition to injection-site sarcomas being produced, subcutaneous injection of cadmium chloride, even at a distance from the testes, often induced testicular necrosis followed by Leydig cell regeneration and hyperplasia and ultimately Leydig cell tumors (Haddow _et al_., 1964; Roe _et al_., 1964; Guthrie, 1964; Gunn _et al_., 1963, 1964, 1965, 1967; Nazari _et al_., 1967; Favino _et al_., 1968; Knorre, 1970, 1971; Lucis _et al_., 1972, Reddy _et al_., 1973). The Leydig cell tumors thusly produced have often been found to be functionally active in the sense of secreting large amounts of sex steroids (Gunn _et al_., 1965; Favino _et al_., 1968; Lucis _et al_., 1972; Reddy _et al_., 1973). Typically, high-level, systemic-injection doses have been employed to produce injection-site sarcomas or distal-site tumors, with effective doses of cadmium often exceeding 1.0 mg/kg of body weight.

Leydig cell tumors observed after systemic injections of cadmium in the above manner, however, have not yet been found to increase in incidence when cadmium is administered orally at lower dose levels (Schroeder _et al_., 1965; Kanisawa and Schroeder, 1969; Levy and Clack, 1975; Levy _et al_., 1975). Schroeder _et al_. (1965) and Kanisawa and Schroeder (1969) exposed rats to cadmium acetate in their drinking water (at 5 ppm) from weaning until death up to four years later and found no significant increase in tumors for cadmium-exposed animals in comparison to the incidence for control animals.

Table 2-8. STUDIES ON CADMIUM TUMORIGENESIS IN EXPERIMENTAL ANIMALS[a]

Author(s)	Animals	Compound and route(s)	Lowest effective dose	Injection site	Tumor site	Type of tumors
Heath *et al.*, 1962	Rats	Cd powder in fowl serum (im[b])	One dose of 0.014 gm	Thigh muscle	Thigh muscle and lymph nodes	Sarcomas
Heath and Daniel, 1964	Rats	Cd powder in fowl serum (im)[b]	One dose of 0.014 gm	Thigh muscle	Thigh muscle and lymph metastases	Sarcomas
Kazantzis, 1963	Rats	CdS (sc)[b]	Two doses of 25 mg ea.	Dorsal sc[b] tissue	Injection site	Sarcomas
Kazantzis and Hanbury, 1966	Rats	CdS (sc)[b]	One dose of 25 mg	Dorsal sc[b] tissue	Injection site plus lung, spleen, stomach, and pancreas	Sarcomas
		CdO (sc)[b]	One dose of 25 mg	Dorsal sc[b] tissue	Injection site	Sarcomas
Haddow *et al.*, 1964	Rats	$CdSO_4$ in rat ferritin (sc)[b]	Ten doses of 20 mg ea.	Right flank	Right flank	Sarcomas
		$CdSO_4$ (sc)[b]	Ten doses of 0.5 mg ea.	Right flank	Right flank and Leydig cell	Sarcomas; Leydigomas
Roe *et al.*, 1964	Rats	$CdSO_4$ (sc)[b]	Ten doses of 0.5 mg ea.	Flank	Flank and testis	Sarcomas; Leydigomas
Guthrie, 1964	Chickens	$CdCl_2$ (intercostal injection)	One dose of 2% solution; amount not given	Intratesticular via intercostal injection	Testis	Teratoma

Table 2-8 (continued). STUDIES ON CADMIUM TUMORIGENESIS IN EXPERIMENTAL ANIMALS[a]

Author(s)	Animals	Compound and route(s)	Lowest effective dose	Injection site	Tumor site	Type of tumors
Gunn et al., 1963	Rats; Mice	$CdCl_2$ (sc)[b]	One dose of 0.03 mmole/kg (3.372 mg/kg)	Subcutaneous (--)[c]	Testis (interstitial cell)	Interstitial cell tumors
Gunn et al., 1964	Rats	$CdCl_2$ (intracapsular)	One 0.4 ml dose of 0.03 M (equivalent to 1.35 mg (d ion)	--[c]	Injection site; testis (interstitial cells)	Sarcomas and Leydigomas
Gunn et al., 1965	Rats	$CdCl_2$ (sc)[b]	One dose of 0.03 mmole/kg (3.372 mg/kg)	Subcutaneous (--)[c]	Testis	Interstitial cell tumors
Gunn et al., 1967	Rats	$CdCl_2$ solution	One dose of 0.17 Cd ion	Ectoderm; intracutaneous (chest); endoderm; salivary gland; liver; ventral prostate; epithelial mesoderm; kidney; mesenchymal mesoderm, sc[b] (intracapsular); im[b] (thigh); subperiosteal (femur)	Subcutaneous	Sarcomas
Schroeder et al., 1965	Rats; mice	Cd-acetate (drinking water)	5 ppm Cd in drinking water	Diet	Similar to controls	Similar to controls

Table 2-8 (continued). STUDIES ON CADMIUM TUMORIGENESIS IN EXPERIMENTAL ANIMALS[a]

Author(s)	Animals	Compound and route(s)	Lowest effective dose	Injection site	Tumor site	Type of tumors
Kanisawa and Schroeder, 1969 Nazari et al., 1967 Favino et al., 1968	Rats	$CdCl_2$ (sc)[b]	--[c]	--[c]	--[c] and testis	Sarcomas and Leydigomas
Knorre, 1970	Rats	$CdCl_2$ (sc)[b]	Equivalent to ~5.5 mg/kg	Left hip	Skin and muscle at injection site	Sarcomas
Lucis et al., 1972	Rats	$CdCl_2$ (sc)[b] intrahepatic	0.02 mM/kg (2.248 mg/kg)	--[c]; liver	Injection site; testis	Sarcomas and Leydigomas
Reddy et al., 1973	Rats	$CdCl_2$ (sc)[b]	0.03 mmole/kg (3.372 mg/kg)	--[c]	Testis	Leydigomas
Levy et al., 1973	Rats	$CdSO_4$ (sc)[b]	Weekly injections of 0.05 mg ea. for 2 yr	Flank	Flank	Sarcoma and other neoplasms
Levy et al., 1975	Rats	$CdSO_4$ (stomach tube)	Weekly injections of up to 4 mg/kg for 18 mo	Diet via tube	--[c]	No tumorigenic effect

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[a] Adapted from Sunderman, 1977.
[b] Intramuscular: im; subcutaneous: sc.
[c] Information unavailable: --

Also, in the studies by Levy and coworkers, cadmium sulfate was administered to rats by direct gastric intubation 3 times per wk for 2 yr (at doses of 0, 87, 180, or 350 μg Cd/kg) and to mice by the same procedure carried out once per wk for 18 mo (at doses of 0, 0.44, 0.88, or 1.75 mg Cd/kg). No significant increases in the incidence of Leydig cell tumors were found for the cadmium-treated animals, nor were any prostate neoplasms or pre-neoplastic changes in the prostate seen in the cadmium-exposed groups. These results are in contrast to findings obtained with intravenous administration of cadmium salts. The authors suggested that low gastric absorption of cadmium and a high spontaneous incidence of Leydig cell tumors in their control group rats, which would overshadow any effect due to cadmium exposure, as possible reasons for no significant response in their study.

The Schroeder and the Levy studies cited above that found no tumorigenic effects after oral cadmium administration have been found to be inconclusive, as evaluated by other working groups (IARC, 1976; Carcinogen Assessment Group, 1977) and the present authors. The doses employed in the various Schroeder and Levy studies resulted in kidney concentrations of cadmium below those typically seen in adult humans. Lastly, certain problems associated with only some animals being sampled for possible tumor pathology and some results being stated only in qualitative terms rather than quantitatively make adequate interpretation of aspects of the studies very difficult.

Based on the collection of other, positive results discussed here, it appears that tumorigenic effects can be induced by cadmium following its systemic injection at very high concentration levels, with sarcomas commonly occurring at the injection site or Leydig cell tumors developing at a distance from the injection site. This latter effect in particular has been taken (IARC, 1976; NIOSH, 1976; Carcinogen Assessment Group, 1978) as providing some evidence of carcinogenic potential for cadmium.

2.15.3 Human Carcinogenesis Studies

The mutagenic and tumorigenic effects discussed above provide some presumptive evidence for cadmium being a carcinogen in humans. Only a relatively limited number of studies, however, have provided any relevant data on possible cadmium-induced carcinogenicity in humans. Such studies are reviewed in more detail in the later chapter on Human Epidemiology (3.7). Therefore, no effort will be made here to review the relevant literature beyond presenting a few summarizing statements and conclusions.

Several epidemiologic studies dealing with increased cancer rates associated with occupational cadmium exposure form a major portion of the existing data base upon which assessments of cadmium-induced human carcinogenicity presently depend. Most of those studies have previously been evaluated or commented on by other work groups (IARC, 1976; NIOSH, 1976; Carcinogen Assessment Group, 1978; Troast, 1978) and include: the Potts (1965) and Kipling and Waterhouse (1967) studies on the same population of workers exposed to cadmium in a battery manufacturing plant; (2) the study of Lemen et al. (1976) on cadmium-smelter workers; (3) the study of McMichael et al. (1976) on rubber-industry workers; (4) the study by Kolonel (1976) on cancer patients, and (5) the study of Kjellström et al. (1979) on battery plant employees. Some of these studies, e.g. that of McMichael et al., were not primarily designed to investigate cadmium effects, but such effects were evaluated retrospectively.

While the above studies differ in regard to the industrial setting in which cadmium or other possible carcinogens were encountered and vary in their methodological soundness, some striking findings become apparent when their results are summarized together as is done below in Table 2-9. As

Table 2-9. SUMMARY OF RESULTS OF HUMAN EPIDEMIOLOGIC STUDIES OF CANCER EFFECTS ASSOCIATED WITH OCCUPATIONAL EXPOSURES TO CADMIUM

Population group studied	Cadmium compound exposed to	Incidences of all cancers	Incidences of lung cancer	Incidences of Prostate cancer	Reference
Battery factory workers	Cadmium oxide	High	Normal	High	Potts (1965)
Battery factory workers	Cadmium oxide	Normal	Normal	High	Kipling and Waterhouse (1967)
Cadmium Smelter workers	Cadmium oxide, others	High	High	High	Lemen _et_ _al_., (1976)
Rubber Industry workers	Cadmium oxide	High	Normal	High	McMichael _et_ _al_. (1976)

seen in that table, each study reports increased incidences of various cancers among the workers studied. Consistent across all of the studies, however, is the finding of higher than normal rates of prostatic cancer. Statistically significant results supporting this were obtained in two of the studies, by Kipling and Waterhouse (1967) and Lemen et al. (1976), while McMichael et al., (1976) reported an apparently high correlation between cadmium exposure and excess prostatic cancer mortality that was not tested by thorough statistical analyses. In each of the above studies, exposure to cadmium oxide occurred as a common element associated with high prostatic cancer rates; some evidence, therefore, appears to exist for cadmium salt possibly being carcinogenic in humans with a predilection for the prostate as a site of action. Somewhat elevated (but not statistically significantly increased) prostatic cancer rates were also reported by Kjellström et al. (1979) in discussing preliminary results of an epidemiology study on cadmium-nickel battery and cadmium-copper alloy plant employees; the final results covering the entire study population, however, remain to be completed and published.

Certain "medical geography" studies have been reported (Troast, 1978) as providing additional data linking cadmium exposure to cancer. For example, Berg and Burbank (1972) related incidences of different types of cancers to cadmium levels encountered in water in major water basins of the United States and found that cadmium levels of 3 μg/l (the recommended safety limit is 10 μg/l) were positively correlated with increased incidences of cancer in those geographic areas. These included cancers of the larynx, pharynx, esophagus, intestine, lung, and bladder; but no data on prostatic cancer incidence were reported. Calculations easily demonstrate, however, that the water levels reported in the Berg and Burbank study and usual levels of water consumption are insignificant in comparison to average normal dietary intake (see Chapter 4).

Also, the Berg and Burbank study failed to control for smoking as a potentially confounding factor. Another study (Zyka, 1973) of cadmium in drinking water in Czechoslovakia has been reported (Troast, 1978) as yielding evidence for high levels of trace metals such as cadmium being associated with increased evidences of cancer. Careful inspection of the Zyka (1973) report, however, shows that no association between cadmium and cancer was established (see CAG, 1978).

2.16 INTERACTIONS OF CADMIUM WITH OTHER METABOLIC FACTORS

The extent to which cadmium imparts a toxic effect in man and animals is highly influenced by the status of the organism with reference to a number of essential chemical elements. Scattered throughout the preceding discussion on cadmium's adverse systemic effects are references to the influence of zinc, calcium, and iron. Mention was also made of some of the mechanisms by which these interactions come into play: by metallothionein induction, modification of absorption, etc. Still, it would be appropriate to summarize in a discrete section the nature of these interactions in a general fashion. Recent reviews (Sandstead, 1977; Nordberg, 1976) include a discussion of cadmium-nutrient interactions. Zinc-cadmium relationships have been discussed in considerable detail in the recently published NAS-NRC document, Zinc (1978); in particular, the data from experimental animals have been comprehensively covered.

2.16.1 Zinc

Deficiency of zinc, a nutritionally required metal, increases the toxicity of cadmium. Conversely, increased levels of zinc tend to offset the harmful effects of cadmium.

The protective effect of zinc against testicular necrosis caused by cadmium (Parizek, 1957) was one of the earliest examples of a cadmium-nutrient interaction to be demonstrated. While protection by pretreatment with zinc would suggest a mechanism involving zinc induction of metallothionein, the cadmium-binding, low-molecular-weight protein; the equal protective efficacy with coadministration of zinc with cadmium would suggest an alternate mechanism, since some induction-time interval would be necessary for metallothionein biosynthesis. Direct zinc-cadmium competition for ligating sites are more plausible in the latter case (Petering, 1971).

A number of studies have indicated that the absolute amounts of either zinc or cadmium are less important than a cadmium/zinc ratio. This certainly appears to be the case with the hypertension experimentally induced by cadmium (see Cardiovascular Effects section). In man, it is known that there is an increase in the cadmium/zinc ratio in hypertensive subjects (Schroeder, 1967; Lener and Bibr, 1971) which probably reflects a loss of zinc. Furthermore, levels of cadmium and zinc in human kidney increase with aging in parallel and in equimolar amounts in the general population (Nordberg, 1976).

The cadmium/zinc relationship may also be synergistic as well as antagonistic in that animal studies on hypertension show both effects appearing across a spectrum of dietary zinc levels (Sandstead, 1976).

2.16.2 Selenium

A number of studies have demonstrated the protective effect of selenium, an essential element, against cadmium toxicity. A demonstration of this element's protective action on cadmium toxicity was the observation of Kar *et al*. (1960) that co-administration with cadmium prevented testicular necrosis. In addition to testicular protection, selenium abolishes the toxic effects of cadmium on ovaries, placenta, and fetal development. It also elevates the LD_{50} and prevents experimentally induced hypertension in a number of species (Sandstead, 1977; Parizek, 1971).

Several recent studies have been directed toward elucidating the mechanism(s) by which selenium exerts a protective effect. Magos and Webb (1976) studied the effect of co-administration of equimolar amounts of selenium and cadmium parenterally on the transport pattern of either element in adult rats and were led to rule out the in vivo formation of cadmium-selenium complexes on a number of grounds, one of which was the cadmium/selenium ratio in kidney.

Gasiewicz and Smith (1976) used ^{75}Se and ^{109}Cd as tracers to study the binding of both elements after simultaneous subcutaneous administration up to 24 hours after injection. Over this time period, the tracers appear in a one-to-one ratio in protein fractions of 130,000 and 330,000 daltons as well as a 420,000-dalton fraction. In vitro studies indicate that selenite does not interact directly with cadmium or plasma proteins but is modified to a form that interacts in a one-to-one ratio with cadmium to form a protein complex of 130,000 daltons.

Stowe (1976) studied the effect of selenium on the movement of cadmium through the biliary tract using bile-duct-cannulated rats. Two mg/kg of selenium were given 3 days prior to cadmium administration and following cannulation. There was a significant increase in the biliary excretion of cadmium. Elevated bile levels following selenium pretreatment are consistent with elevated blood cadmium levels and reduced amounts in the liver (Gunn et al., 1968). According to Stowe (1976), it is likely that cadmium present in bile is not associated with metallothionein; but the more unstable, higher molecular-weight fraction which also binds cadmium is stimulated by selenium and is present in testicular tissue (Chen et al., 1974).

Prohaska et al. (1977) studied the relationship in rats among cadmium, selenium, and glutathione peroxidase, a selenoprotein. Rats given a dose of cadmium sufficient to induce a just-visible hemorrhagic response (0.011 mmole/kg, administered subcutaneously) in the testis showed elevated levels of the enzyme. This may be a vasculopathic effect with the increase in activity arising from erythrocyte enzyme via leakage into the testes, enzyme levels in red blood cells being much greater than in testicular tissue. Isolation of the main fractions of the enzyme using labeled cadmium and selenium showed no cadmium-enzyme binding, and these fraction activities were not inhibited by cadmium *in vitro*. Pretreatment with selenium showed most of the radiolabelled cadmium (^{109}Cd) to be shunted from proteins of low molecular weight (15,000 and 34,000) to a peak with molecular weight 110,000, a selenoprotein. The role of this shifting in testicular protection remains to be demonstrated. Prohaska et al. (1977) found that the postulated role of the cadmium-binding protein of molecular weight 34,000 in testicular injury was not apparent in their animals. Animals not having analyzable protein of this weight sustained testicular injury while older animals showed the protein present with or without concomitant injury. The critical concentration for testicular damage was reported to be 150 nanograms/gram wet weight, above which evidence of injury occurs.

Piotrowski et al. (1977) studied the effect of selenium on cadmium binding to metallothionein. Selenium was found to have little effect on the induction of hepatic metallothionein by cadmium under conditions of repetitive dosing. This may be contrasted to the data of Chen et al. (1975a) who demonstrated an effect in kidney and testes in the direction of higher-weight binding protein.

2.16.3 Calcium

Discussion of a number of interrelationships between calcium and cadmium have been included in other parts of this document, so additional data will be only briefly summarized here.

Calcium deficiency is known to increase the intestinal absorption of cadmium and its subsequent deposition in tissue (Larsson and Piscator, 1971; Itokawa et al., 1974, Pond and Walter, 1975; Washko and Cousins, 1976). Washko and Cousins (1977) found that cadmium retention and signs of toxicity are enhanced by feeding a low calcium diet and that the increased calcium binding protein activity observed is responsible for the increased cadmium uptake. Earlier studies on swine (Hennig and Anke, 1964) and chick (Stancer and Dardzonov, 1967) showed that cadmium has an inhibiting effect on calcium deposition in bone even when calcium is present at normal levels. These doses, however, were extremely high. Data presented in the section on gastrointestinal effects indicate that the absorption effect is imparted in the intestinal epithelium. Effects on Vitamin-D metabolism were discussed in the Sub-Cellular Effects section.

2.16.4 Iron

In the Hematological Effects section it was pointed out that the anemia occasioned by cadmium can be offset by dietary supplementation with ferrous salts.

In the study of Hamilton and Valbert (1974), cadmium fed to rats with restricted iron intake caused a decrease in the uptake of tracer iron (^{59}Fe). As little as 10 ppm cadmium in drinking water had a demonstrable effect, and the data indicate that cadmium competes with iron at one or more steps of iron transport, probably the initial uptake step as shown in duodenal-perfusion experiments. The effect of cadmium on iron absorption bears important implications for man, since persons with iron deficiency might absorb more cadmium than those with normal iron stores. Flanigan et al. (1978) assessed the effect of iron deficiency on increased dietary cadmium in mice and human subjects. Mice fed a low-iron diet and cadmium (10 μM; 1.1 ppm) in drinking water showed impaired growth and accentuated anemia development, while the normal-iron animals showed no effects at the same cadmium-exposure level. Furthermore, the iron deficiency led to increased cadmium levels in the duodenal mucosa and the kidney. In human subjects; experiments using radiolabelled cadmium (^{115m}Cd) showed that individuals with low iron stores absorbed 8.9 μg of 25 μg cadmium given, while the value for individuals with normal iron was 2.3 μg. In human subjects with iron deficiency, an approximate four-fold increase in absorption of cadmium will occur.

2.16.5 Copper

Early evidence for the effect of cadmium on copper metabolism was the observation that dietary cadmium (100 ppm in drinking water) induced aortic morphological abnormalities in chicks which closely resembled the effect of copper deficiency (Hill, 1963). Other effects include the impairment of collagen and elastin linking (Ruchker *et al*., 1971), a copper-mediated process, and reduction of plasma ceruloplasmin in rats (Campbell and Mills, 1974).

In the study of Irons and Smith (1976), simultaneous administration of copper and cadmium yielded a redistribution of cadmium with little incorporation into metallothionein. This may explain, in part, the synergistic effect of copper when both are given together. The data suggest that retarded incorporation into metallothionein occurs via copper-mediated aggregation of this protein, an *in vivo* confirmation of demonstrated *in vitro* aggregation (Bremner and Young, 1976).

In contrast, combining copper with zinc and manganese has the joint effect of reducing cadmium accumulation in quail (Fox, 1976).

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3. HUMAN EPIDEMIOLOGY

3.1 INTRODUCTION

Studies directly relating cadmium exposures to human health effects in various population groups are required to define the levels of exposure at which adverse health effects appear in order to identify population segments at high risk. To date, such studies have mainly been limited to examination of occupationally exposed workers and population groups in areas of Japan where Itai-Itai disease has been found. Few such studies have been carried out, however, for the general American population--especially concerning health effects associated with exposures to cadmium in the ambient environment. It is thusly necessary, based on available data, to construct a logical framework or chain of interrelationships from external cadmium exposure through absorption and retention of cadmium to associated adverse health effects for American populations. This can be accomplished by: (1) delineating the distribution of cadmium to which humans are exposed and determining the contribution of various sources to the overall multimedia exposure of American population segments; (2) assessing levels of cadmium in blood or urine or other indices of internal absorption and retention in various population segments; and (3) correlating these findings with research results associating adverse health effects with particular levels of absorption or retention of cadmium in other population groups. An analysis of exposure sources and levels alluded to in (1) above is provided later, in Chapter 4, as part of an overall risk assessment discussion. Background information pertaining to the latter two items above, i.e., (2) and (3), however, is presented below, before consideration of the most salient points as part of the risk assessment discussion in Chapter 4.

3.2 CADMIUM IN BLOOD AND URINE OF HUMAN POPULATIONS

Epidemiologic studies of cadmium levels in human blood and urine have been carried out in an effort to index cadmium exposure and asorption in both normal population segments and population groups with known high cadmium exposures.

The data for blood and urine cadmium levels in so-called "normal" populations presented here must be viewed with great caution for several reasons. The definition of "normal" varies enormously from study to study. Frequently, it is defined as "no known occupational exposure", but little evidence is presented to show how this was defined or established for the subjects. At times, the "normal" study group is drawn from patients who are believed to be free of disease since they require elective surgery, have had accidents, or are in other ways deemed to be free of metabolic or chronic disease. Finally, many of the population surveys were primarily designed to study other pollutants, and the selection of the study population was stratified to represent gradients of the other pollutants in a single source such as air, lead paint, etc. Since cadmium does not always arise from the same sources as other pollutants, such stratification may in fact produce a biased rather than a random selection of the study population as far as cadmium is concerned.

Rapid changes in laboratory techniques also present a problem. Findings from earlier studies may not be comparable to those for more recent ones. In fact, many investigators comment that variations in the findings from different studies may be due primarily to variations in methodology. Sampling variations for the same individual must be added to this variance.

Variance within data for a single study should also be considered. It arises from so-called "within-group variance," which is due to differences among the subjects such as age, sex, exposure, etc. and also from biological differences in subjects within each of those same categories. Investigators, particularly the earlier ones, do not always provide information so that these sources of variance may be assessed.

3.2.1 Sources of Variations in Human Blood Cadmium Levels

A number of factors appear to affect human blood cadmium levels. Among the sources of variation discussed here in detail are demographic factors and geographic variation.

Quantitative measurements of cadmium at the levels encountered in biological media such as blood and urine are methodologically difficult, chiefly due to matrix effects. The extent of interference posed by the biological matrix will vary from method to method. At present the most common way to assess cadmium levels in blood and urine is atomic absorption spectrometric analysis, a method with a number of problems.

Blood samples which are directly analyzed by atomic absorption spectrometry using the Delves Cup or the furnace technique may yield rather high cadmium values if care is not taken to adequately correct for smoke or other signal artifacts. Similar care must be exercised when anodic stripping voltammetry is employed, since the electrochemical behavior of the element is sensitive to the presence of ligating groups in the medium. Where feasible, it is probably most desirable to isolate cadmium from the matrix in which it occurs, using a solvent-extraction step.

An added problem is that of contamination of the blood or urine samples, particularly contamination of blood in collection tubes with cadmium-containing stoppers.

3.2.1.1 Demographic variability in human blood cadmium levels--Data relating age, sex, and race to human blood cadmium levels are very scarce. Only a few studies, for example, have been reported concerning blood cadmium values for children.

Ediger and Coleman (1973) recorded blood cadmium concentrations for 60 children. The major focus of the work reported was on the analytic methodology and no descriptions of demographic characteristics of the study sample were given. A median blood cadmium concentration of 0.05 μg/dl was reported.

Bogden *et al*. (1974) analyzed blood from 369 children being screened for lead poisoning in Newark, New Jersey. The children's ages ranged from 1 to 8 yr. Mean blood cadmium concentration was 0.3 μg/dl (no standard deviation given) with a range of 0.0 to 2.8 μg/dl. These children constitute a high-risk group for lead poisoning and are from inner-city ghetto sections with old and dilapidated housing. Race was not reported, but it seems safe to assume that many were Black.

Smith *et al*. (1976b) examined blood cadmium levels for 26 hospitalized boys and girls aged 2 mo to 13 yr (mean age 4.9 yr). These were white middle- and upper-middle-class children from Salt Lake City, Utah, who were hospitalized for elective surgery such as tonsillectomy. The mean value for blood cadmium levels was 0.66 ± 0.25 μg/100 gm with a range of 0.21 to 2.64 μg/100 gm.

Rosmanith *et al*. (1975, 1977) reported findings from a survey of 413 children from a north German industrialized town. The children, with an age range of 2 to 14 yr, were invited for examination according to a selection method based on their birthdate. The total population of 2 to 14 yr old children was estimated at 9,000; and 600 were selected to constitute the sample, with a response rate of 69 percent. The authors reported a mean blood cadmium level of 0.11 ± 0.23 μg/dl. Age and sex did not prove to be significant variables.

Delves *et al*. (1973) compared children with suspected lead poisoning and a hospitalized control group not suspected of having lead intoxication and having no anemia, pica, mental retardation, or convulsions. These 89 control children were 4 days to 15 yr old, were both male and female, and had a mean blood cadmium value of 0.49 ± 1.5 μg/dl with range of 0.0 to 1.9 μg/dl. The lead-poisoning-suspected "case" group consisted of 189 boys and girls, aged 2 mo to 15 yr and with proportionately more children in the 3- to 6-year age category than controls. The mean value for "cases" was 0.57 μg/dl (no standard deviation given), and the range was from 0.0 to 7.9 μg/dl. The difference for the two exposure groups was not statistically significant. Differences by age and sex were also not significant.

In summary, there seems to be no age gradient among children's values for blood cadmium concentrations as, for example, has been found for blood lead concentrations where younger children show higher concentrations than older ones under the same exposure conditions. The explanation for the differences in the absolute values reported in the various publications is not apparent from the data reported. Nevertheless, the mean blood cadmium values reported for children are consistently below 1.0 μg/dl and do not differ much from most values reported for "normal" adults.

When examining the blood cadmium concentrations reported for adults, it is important to note the recent custom of reporting separate values for smokers and nonsmokers. Invariably, regardless of the definitions utilized to categorize "smokers" and "non-smokers," the smokers have been found to have higher blood cadmium values. Further, it should be noted that most of the study populations are small and authors frequently neither report nor analyze the effect of age categories within their study groups. Equally frequently, sex differences are not reported when both sexes are represented in the study group.

Several reports have been omitted from the tabular presentation (Table 3-1) below because of the problems encountered in interpreting their findings.

The largest normal population evaluated, the 1954 military recruits from a Chicago induction center, has been omitted from this table. Creason et al. (1976) found a mean value of 5.0, a median value of 3.6, and a range of 1.0 to 30.0 μg/dl for these men aged 18 to 24. They speculate that the latter high value, which is not approached by any others reported for non-exposed populations, is probably due to contamination of blood samples from the containers used for storage since the materials were stored for about one and one-half years before analysis.

Also omitted from the table was the "19 cities" study. Kubota et al. (1968) selected 243 male residents from 19 cities in 16 states in the United States. Mean blood cadmium concentration was 1.77 μg/dl and the range was 0.5 to 14.6 μg/dl. The analytic technique used made it impossible to detect values under 0.5 μg/dl, and 111 subjects had such low values. This left 132 determinations. The authors stated that more than half of the determinations were $\leq$ 0.5 μg/dl and that the median was "about" 0.5 μg/dl.

Willden and Hyne (1974) reported on 19 male and 16 female controls who are described as "normal" adults. These investigators did not control for background in their procedure.

Table 3-1 shows the findings from the more recent studies which either evaluated "normal" adults or selected "normal" controls for some study or

Table 3-1. "NORMAL" BLOOD CADMIUM LEVELS
(μg/dl)

Location	N(sex)	SS^{a,b}	Age^{a}	Mean ± SD^{b}	Range	Procedure	Reference
Children							
U.S.							
Oklahoma City, OK	60(both)	--	12	Median = 0.05	--	Background corr.	Ediger and Coleman, 1973
Newark, NJ	369(both)	--	1-8	0.3	0.00-2.8	AA^{d}: extraction hemolysates by APDC-MIBK procedure	Bogden et al., 1974
Salt Lake City, Utah	26(both)	--	2 mo.-13 yr.; x = 4.9	0.66 ± 0.25	0.21-2.64	AA^{d}: wet ashed samples extracted with Dithizone/Chloroform	Smith et al., 1976
Denver, CO	25(both) 25(both) 25(both)	-- -- --	1-4 5-9 10-19	0.12 ± 0.15^{c}	< 0.04-1.77^{c}	Flameless AA^{d}: modified Delves cup procedure	Wysowski et al., 1978
Germany Northern Industrial town	413(both)	--	2-14	0.11 ± 0.23	--	AA^{d}: Delves cup procedure	Rosmanith et al., 1977
England Urban	89(both)	--	4 days-15 yr.	0.49 ± 1.50	0-1.9	AA^{d}: wet ashed sample	Delves et al., 1973
Adults							
U.S.							
"working males"	153(M)	--	14->65	0.85; median = 0.70	0.34-5.35	Emission spectroscopy of wet ashed samples	Imbus et al., 1963
S. Carolina workers in a lumber mill	40(M)	--	<39->60	0.42 ± .07	--	AA^{d}: flame procedure on plasma	Hammer et al., 1972

Table 3-1 (continued). "NORMAL" BLOOD CADMIUM LEVELS
(μg/dl)

Location	N(sex)	$SS^{a,b}$	Age^{a}	Mean ± SD^{b}	Range	Procedure	Reference
Oklahoma City, OK	50(-)	--	Adults	0.06	0.02-0.2	Delves cup	Ediger and Coleman, 1973
Denver, CO	25(both)	--	20-39	0.12 ± 0.15^{c}	$<0.04\text{-}1.77^{c}$	Flameless AA^{d}: modified Delves cup procedure	Wysowski et al., 1978
	25(both)	--	≥40				
Houston, TX	41(M)	--	19-53	0.7 ± 0.85	--	AA^{d}: with correction direct sample analysis	Johnson et al., 1974; 1975
	27(M)	--	22-50	0.4 ± 0.44	--		
	36(F)	--	21-32	0.8 ± 1.70	--		
Belgium							
"workers"	33(M)	S	48±10	0.7 ± 0.6	--	Extraction	Lauwerys et al., 1973
	11(M)	NS	31±14	0.7 ± 0.3	--		
	14(M)	S	30±7	1.2 ± 1.5	--		
	15(M)	NS	28±9	0.8 ± 1.8	--		
"workers"	22(M)	S	51±2	0.70 ± 0.10	--	Extraction	Lauwerys et al., 1974
"workers"	110(M)	--	Adults	0.58 ± 0.21	--	Extraction	Roels et al., 1974
Germany							
village	66(both)	S	Adults	0.33 ± 0.19	0.10->0.8	AA^{d}: Delves cup procedure	Einbrodt et al., 1976
village	103(both)	NS	Adults	0.22 ± 0.08	<0.1-0.49		
West Germany							
--	37(both)	--	Adults	0.95	0.4-1.9	Flameless AA^{d} of hemolysates	Stoeppler et al., 1974

Table 3-1 (continued). "NORMAL" BLOOD CADMIUM LEVELS (μg/dl)

Location	N(sex)	SS[a,b]	Age[a]	Mean ± SD[b]	Range	Procedure	Reference
Sweden							
--	25(M)	S	20-55	0.23	0.06-0.61	Background corr.	Ulander and Axelson, 1974
--	19(M)	NS	20-55	0.06	0.03-0.12		
--	20(F)	S	20-55	0.20	0.05-0.76		
--	25(F)	NS	20-55	0.05	0.02-0.10		
Denmark							
--	110(both)	--	0-80	1.26	0.5-4.5	Graphite atomizer	Nygaard, 1974
--	31(M)	--	21-71	1.64 ± 0.85 (combined)	0.3-4.8 (comb.)	Flameless AA[d]	Clausen and Rastogi, 1977a; 1977b
	23(F)	--	21-73				
Scotland Renfrew	34(F)	--	58.6±6.4	0.27 ± 0.19	--	AA[d]: APDC-MIBK extraction of hemolysates	Beevers *et al.*, 1976a
	36(M)	--	58.6±6.3	0.20 ± 0.13	--		
	35(both)	S	45-64	0.32 ± 0.16	--		
	35(both)	NS	All	0.18 ± 0.08	--		
Holland Arnheim	84(F)	NS	20-50	$\bar{X}g$ = 0.04	0.02-0.25	Flameless AA[d]	Zielhuis *et al.*, 1977
	61(F)	LS	20-50	$\bar{X}g$ = 0.06	0.2-0.24		
	77(F)	HS	20-50	$\bar{X}g$ = 0.07 (0.2 calculated as 0.1)	0.02-0.44		

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[a] Information not published is indicated by --.

[b] SS: smoking status; S: smokers; NS: non-smokers; LS: light smokers; HS: heavy smokers.
SD: standard deviation. Arithmetic means are given unless indicated by $\bar{X}g$ to note geometric mean.

[c] Determined for all groups combined

[d] AA: atomic absorption

patient group. Concentrations grouped according to sex of subject are indicated, where possible, in Table 3-1. Generally there is good agreement among the concentrations reported within studies: that is, males and females do not appear to show different concentrations within a given study and virtually all values reported fall below 1.0 µg/dl*. The studies which included both sexes but reported total means only also appear to be in the same range. Smokers show concentrations which are significantly higher in each study.

It is difficult to interpret the differences among various study findings; most likely they are due to variation in methods of analysis. There are not enough studies from any one country, except perhaps the United States, to consider the question of differences among countries. It is quite possible that smoking habits vary among different countries for males and females and for urban and rural populations.

Some additional studies investigated members of "normal" population segments selected for study of cadmium or combinations of cadmium and other heavy metals.

Imbus _et al_. (1963) studied chromium, boron, and nickel as well as cadmium in the blood of 154 volunteers. These consisted of 100 workers selected from among Cincinnati, Ohio, employees of 15 companies and nearby farms. An additional 54 men were selected from metropolitan New York, Denver, Miami, and Portland, Oregon. Altogether, 18 types of industries were represented. The distribution of age and occupational categories approximately corresponds to the U.S. male working population. The median for blood cadmium concentration was 0.70

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*Note that blood cadmium levels of 1.0 µg/dl are equal to 1.0 µg/100 ml or ~9.0 nmol/l, with the latter mode of expression conforming to a usage convention adopted by European investigators in recent years.

µg/100 g, the mean 0.85, and the range 0.34 to 5.35 with the 95th percentile at 1.68 µg/100 g.

Hammer et al. (1972) evaluated workers with three levels of occupational exposure to cadmium. These were all Black males from South Carolina. The low-exposure group worked in a lumber mill, while exposed groups worked either continuously or intermittently exposed to cadmium in a plant producing superphosphate fertilizer. Mean plasma cadmium concentration for the 40 low-exposure group subjects was 0.42 ± 0.7 µg/dl, lower than that for the two higher exposure groups.

Ediger and Coleman (1973), as mentioned above, reported concentrations found in the course of a methodological study. They report a mean concentration of cadmium of 0.06 µg/dl for 50 adults.

The "Houston Study" conducted by Johnson et al. (1975) reported concentrations for controls selected for three groups with risk of exposure to air pollution by working in traffic, in parking garages, or by living near a freeway. The means reported represent four blood samples per individual collected over time, and there was variance between tests for some groups. Controls for traffic policemen (N = 41) aged 19 to 53 yr had a mean concentration of 0.8 ± 0.85 µg/dl, controls for garage attendants (N = 27) aged 22 to 50 yr had a mean of 0.4 ± 0.44 µg/dl, and controls for women living near a freeway (N = 36) aged 21 to 32 yr had a mean of 0.8 ± 1.7 µg/dl.

Three studies from Belgian investigators are in the literature. Lauwerys et al. (1973) reported on exposed and nonexposed factory workers by sex and smoking status. The mean blood cadmium concentration for the nonexposed smokers and nonsmokers by sex are shown in the table. A later report by this group (Lauwerys et al., 1974) showed that 22 male workers selected as nonexposed controls had a mean concentration of 0.7 ± 0.1 µg/dl. Roels _et al_. (1974) reported on concentrations for 110 male workers selected as controls. Mean blood cadmium concentration was found to be 0.58 ± 0.21 µg/dl.

Einbrodt _et al_. (1976) evaluated blood for all 169 adults living in a small North German village known to be without environmental cadmium sources. The findings were presented for smokers and nonsmokers without definition of age at adulthood or further definition of smoking status. Means of blood cadmium concentrations found were 0.22 ± 0.08 µg/dl for nonsmokers, while smokers showed a mean of 0.33 ± 0.19 µg/dl which is a statistically significant difference. Stoeppler _et al_. (1974) reported a mean of 0.95 µg/dl for 37 adults, with a range from 0.4 to 1.9 µg/dl.

Ulander and Axelson (1974) reported concentration means for smokers and nonsmokers. The differences between smokers and nonsmokers were statistically significant as was the difference between younger and older male smokers.

Nygaard _et al_. (1974), using a graphite atomizer procedure, found a mean blood cadmium level of 1.26 µg/dl (range 0.4 to 4.5 µg/dl) in a Danish population of 110 males and females ranging in age from newborn to 80 years old. Clausen and Rastogi (1977a,b) reported on 54 Danish adults. They found a mean blood cadmium of 1.64 ± 0.85 µg/dl with a range from 0.3 to 4.8 µg/dl.

Beevers _et al_. (1976a) reported concentrations for individuals found to be normotensive in a hypertension screening clinic. They were matched by age and sex to hypertensives selected for a study of any association between hypertension and cadmium concentrations. The difference between concentrations for smokers and nonsmokers was significant, but, for hyper- and normotensives, no significant difference was found.

Zielhuis et al. (1977) evaluated the blood cadmium concentrations of 222 housewives from Arnheim, the Netherlands, who were married to blue-collar or lower-income, white-collar workers. All were volunteers, and their smoking status was ascertained. The concentrations and geometric means were the following: 84 non-smokers, 0.04 μg/dl with a range of < 0.02 to 0.25 μg/dl; 61 light smokers (1 to 9 cigarettes/day), 0.06 μg/dl with a range of < 0.02 59 0.24 μg/dl; 77 heavy smokers (≥ 10 cigarettes/day), 0.07 μg/dl with a range of 0.02 to 0.44 μg/dl. (The values < 0.02 were calculated as 0.01 μg/dl.) Non-smokers differed significantly from light and heavy smokers.

Wysowski et al. (1978) studied cadmium exposure in a community near a smelter (Denver, Colorado). Whole blood and urine specimens were obtained from 250 individuals living within 2 km of the smelter, as well as from a control population of 105 residents. Whole blood values, obtained by flameless atomic absorption methods, showed median blood levels of the "smelter" and "control" groups of 0.05 and 0.07 μg/dl, respectively. No statistical significant differences were obtained in the study, except between smokers and non-smokers; that is, smokers had higher blood cadmium values than non-smokers. It should be noted that the mean annual airborne cadmium concentration in the study area about 1 km from the smelter was 0.023 $\mu g/m^3$, whereas the mean air concentration in the comparison area 13 km distant was 0.003 $\mu g/m^3$.

Turning to other areas of known environmental cadmium contamination, recent pilot surveys (Carruthers and Smith, 1979) have been conducted in the vicinity of Shipham, England, an area of cadmium contamination from past zinc-mining activities. The survey revealed that 22 of 31 residents sampled (14 women, mean age 48.9 yr; 17 mean, mean age 50.9 yr.) had blood cadmium levels elevated above normal levels (≅1.0 μg/dl for non-smokers; ≅2.0 μg/dl for smokers). Soil cadmium levels in the Shipham area ranged from 60 to 998 ppm, compared with 60 ppm levels reported for the region around Toyama City in northern Japan, another area of former zinc-mining activity and where extensive studies have probed the relationship between cadmium exposures and Itai-Itai disease endemic in the area.

The Japanese research, however, has not yielded blood cadmium data. Presumably the utilization instead of urine cadmium as the main exposure indicator in the Japanese studies is due to the usefulness of urine analyses in determining proteinuria.

3.2.1.2 Other variation--Only one study (Hecker et al., 1974) compared "acculturated" and "unacculturated" groups: adult volunteer blood donors in Ann Arbor, Michigan, and Yanomamo Indians from the interior of Venezuela. Blood cadmium determinations were done for 47 of the 100 people from Ann Arbor and 90 of the 137 Indians. The values for the Indians were a mean of 1.43 ± 1.19 μg/dl whole blood with a range of 0.3 to 5.7 μg/dl. The Ann Arbor group had a mean of 1.71 ± 1.89 μg/dl and a range of < 0.1 to 9.6 μg/dl. The values are high and probably attributable to the analytic methodology. Clearly these are not enough data to assess blood cadmium levels for populations in remote, non-technologically advanced areas.

Urban and rural differences also cannot be evaluated at this time. There are no studies reporting blood cadmium levels for rural populations.

3.2.1.3 Occupational exposure and blood cadmium--The extensive literature dealing with the effects of high cadmium exposure levels at places of work will not be reviewed here. The cadmium in dust and fumes is inhaled, and exposed personnel have consistently shown levels of blood cadmium concentrations that have been considered to be abnormally elevated. Presumably, faulty hygiene contributes to additional exposure by transfer of dust from hands and clothing to food. Piscator et al. (1976) showed that cigarettes and tobacco handled at work by workers who were exposed to cadmium oxide dust have a higher cadmium content than these smoking materials ordinarily show.

There have been no studies exploring the effect of workers carrying cadmium dust home and contributing to the exposure of other family members, although this possible route of secondary exposure should be assessed in view of recent reports of lead exposure by this route.

3.2.2 Sources of Variation in Human Urine Cadmium Levels

As noted before in the discussion of the determination of blood cadmium values, cadmium measurement in biological media can be fraught with analytical errors. Urine is a particularly vexing medium for trace metal analysis, because of both the high content of inorganic salts and the presence of organic substances. In particular, the atomic absorption analysis of cadmium in urine is complicated by both smoke artifacts and the levels of chloride ion present. Solvent extraction of ashed samples should be carried out where possible.

Studies of the normal population, control, or reference cases cited before also frequently determined concentrations of cadmium in urine. Table 3-2 shows the concentrations found in those studies, as well as those reported by Ross and Gonzalez (1974), Kubasik and Volosin (1973), Tada et al., (1972), Fukabori and Nakaaki (1974), and Miller et al., (1976). The excretion rate for cadmium in urine by normal persons is age dependent. There is an increase until the late fifties, followed by a decline. The mean urine cadmium concentrations reported for the studies listed in Table 3-2 indicate a general daily urine cadmium excretion level between <1 and 2 μg day. The results of the studies listed in the table, however, obscure the effect of age.

Table 3-2. "NORMAL" URINE CADMIUM LEVELS[a]

Location	N(sex)	Age	Mean ± SD	Range	Unit	Procedure	Reference
Children							
German Industrial town	413(both)	2-14	0.50 ± 0.40	--	μg/l	AAS	Rosmanith *et al.*, 1977
Adults							
U.S.							
Cincinnati, Ohio & 4 other met. areas	154(M)	14->65	1.59 ± 4.13 median = 1.15	<0.5-10.8	μg/l	Cholak and Hubbard method	Imbus *et al.*, 1963
S. Carolina	40(both)	<39-60+	1.04	--	μg/l	AAS Parker-Elner	Hammer *et al.*, 1972
--	13(--)	--	2.9	0-10.1	μg/day	Extraction carbon rod atomizer	Kubasik and Volosin, 1973
--	20(--)	--	1.5 ± 0.7	0.4-3.7	μg/l	Graphite atomizer	Ross and Gonzalez, 1974
Houston, TX	27(M) 36(M)	22-50 21-32	0.5 0.6	-- --	μg/l	Acidified urine and Delves cup procedure	Johnson *et al.*, 1974
Houston	41(M)	19-53	0.6 ± 0.44	--	μg/l	Acidified urine and Delves cup procedure	Johnson *et al.*, 1975
Japan							
--	81(--)	20-60	1.39	0.25-4.0	μg/l	Extraction	Tada *et al.*, 1972
--	5(--)	27-37	2.56	1.7-3.7	μg/day	Extraction	Taguchi *et al.*, 1972
--	374(--)	20-60	$\bar{X}_g$'s = 0.64 + 0.65 -0.33	0.05-3.68	μg/l[e]	--	Fukabori and Nakaaki, 1974
			1.06 ± 1.06 -0.33	0.24-6.72	μg/24 hr	--	

Table 3-2 (continued). "NORMAL" URINE CADMIUM LEVELS[a]

Location	N(sex)	Age	Mean ± SD	Range	Unit	Procedure	Reference
Belgium --	33(M)[c]	48±2	2.0 ± 0.2	--	µg/g creatinine	Extraction	Lauwerys et al., 1973
	11(M)[d]	33±4	1.0 ± 0.2	--			
	14(F)[c]	30±2	2.6 ± 0.8	--			
	15(F)[d]	28±2	1.5 ± 0.5	--			
--	110(M)	--	1.79 ± 1.68	--	--	Extraction	Roels et al., 1974
Australia Brisbane	22(both)	Adults	1.1	< 0.5-2.5	µg/1	AAS: APDC-MIBK flameless	Miller et al., 1976

[a] Arithmetic mean unless otherwise indicated; geometric mean: $\bar{X}$g.; information not reported: --.

[b] AAS: atomic absorption spectroscopy.

[c] Smokers.

[d] Non-smokers.

[e] Adjusted individually for specific gravity.

In contrast, two other recent studies provide information on age relationships. Tsuchiya et al. (1976) reported on a study of 609 Tokyo residents which permits analysis of the urine cadmium concentrations by age intervals. Figure 3-1 shows the distribution of mean urine cadmium concentrations by age as well as the standard deviations. The authors also collected data on concentrations of cadmium in the renal cortex, renal medulla, liver, pancreas, heart muscle, and aorta. They examined 169 cadavers of residents of Tokyo with no known disease or poisoning, who had died of accidental causes of death. The analysis of tissue concentrations permitted a calculation of total body burden of cadmium by age. The authors found the mean urine cadmium concentration for ages 30 to 59 yr to be 1.7 ± 1.5 µg/l, with an upper-range value of "about 10 µg/l."

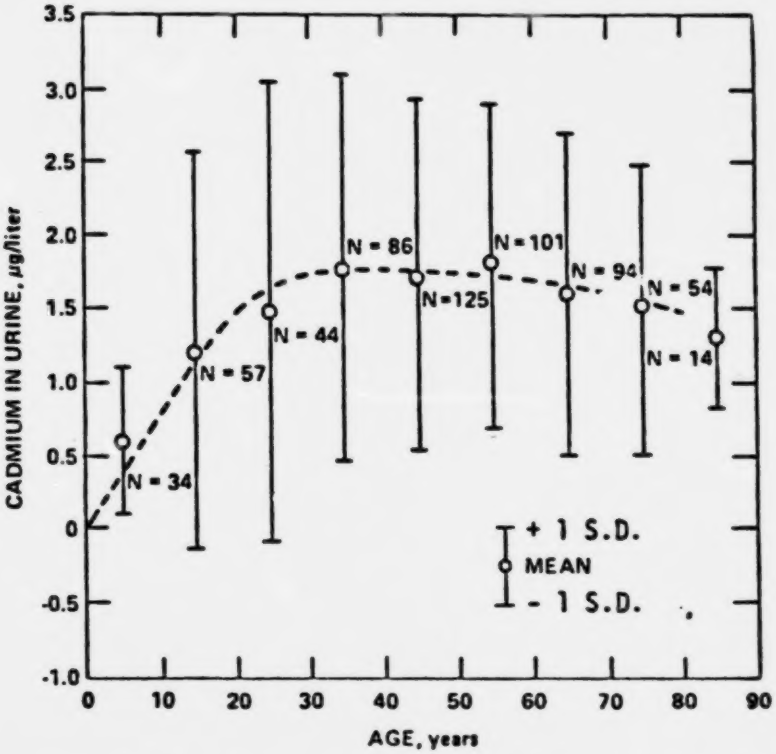

Figure 3-1. Distribution of mean urine cadmium concentrations by age.

Source: Tsuchiya et al.,(1976).

It was pointed out that it is essential that as many cases as possible--more than 20 or 30--within the same sex and age categories be analyzed in order to meet the problem of large individual variation. Johnson et al. (1977) reported urine cadmium concentrations for 86 males in Dallas, Texas, included as part of the collaborative study undertaken in Japan, Sweden, and the United States. Table 3-3 shows their findings. Age-related changes were found in the data with an increase occurring until 40 to 49 yrs and then a subsequent decrease. In another study, by Elinder et al. (1978), cadmium concentration in the urine of 131 Swedes, including 50 pairs of identical twins, were measured. As seen in other studies, urinary cadmium increased with age and was higher among smokers than among non-smokers. The daily cadmium output among non-smokers in various age groups corresponded better with total kidney burden than with daily dietary intake.

Table 3-3. URINE CADMIUM LEVELS FOR "NORMAL" MALES IN DALLAS, TEXAS, DETERMINED BY ATOMIC ABSORPTION[a,b] (μg/l)

Age (years)	N	Geometric mean	Confidence interval
0-9	15	0.415	0.289-0.553
10-19	8	0.334	0.174-0.516
20-29	16	0.422	0.300-0.556
30-39	7	0.496	0.305-0.716
40-49	16	0.797	0.642-0.966
50+	24	0.704	0.582-0.835

[a] From Johnson et al., 1977

[b] 5th to 95th percentile range: 0.148 to 1.293

In the recent report of Tati et al. (1976), involving unexposed Japanese subjects, the age/cadmium-excretion relationship was established using males and females up to 75 yr of age. The distribution of urinary cadmium levels followed essentially a log-normal pattern, with levels increasing with age up to the 60- to 69 yr age group in males and the 50- to 59-year-age group in females. This reflects an increasing body burden with age (Friberg et al., 1974), due to the relatively long half-life of cadmium in major organs estimated to range from 17 to 38 years.

The report of Wysowski et al. (1978), mentioned earlier under Section 3.2.1, on blood cadmium levels in residents living near a smelter also included urine cadmium values of 0.9 μg/l and 0.8 μg/l, respectively, for residents close to a smelter and a control group. No significant differences were found, except for smokers having significantly higher urine cadmium levels than non-smokers.

The literature relating occupational exposure to variations in urine cadmium concentrations will not be reviewed here except to note that it has been suggested that these concentrations may increase when renal tubular damage exists, as indexed by proteinuria and glycosuria. This increase is independent of age. Further, little data exist which relate variations in urine cadmium concentrations to food and water levels of the metal, except for Japanese populations; and these are discussed later in relation to Itai-Itai disease.

3.2.3 Sources of Cadmium Variation in Human Hair

Concentrations of cadmium in hair has been evaluated as an indicator of exposure to the metal. Several studies have been reported where hair cadmium levels have been correlated with environmental exposures. Hammer et al. (1971) analyzed hair samples from fourth-grade boys from five cities rated as varying in overall environmental cadmium levels. The analysis showed that arithmetic and geometric means varied by city in accordance with the city's exposures rating. The geometric means ranged from 2.1 to 0.7 parts per million (ppm).

Pinkerton et al. (1974) analyzed hair samples from three communities which varied in their levels of environmental cadmium. Geometric means of hair cadmium concentrations, while different for each community, did not follow the exposure gradient.

Creason et al. (1975) reported significant correlations between cadmium content of hair and exposure as measured by content in dustfall and housedust in metropolitan New York. The exposure measurements came from the CHESS network, and the three communities showed a gradient for cadmium exposure. A total of 498 participants provided hair samples and sociodemographic information. The geometric mean hair cadmium concentrations in children aged 0 to 15 yr were 0.88 ± 0.42 to 1.85 μg/g. For adults, the values were 0.76 ± 0.33 to 1.74 μg/g. No significant association with exposures were found, however, although other trace metals also evaluated did show such association.

Hambidge et al. (1974) reported on hair trace-metal levels for 18 young adults from Denver, Colorado; 11 from Chandigash, India; and 25 from Bangkok, Thailand. The analytic method for assessing cadmium concentrations gave a detection level of 0.1 ppm; and 48 percent of Denver, 12 percent of Chandigash, and 72 percent of Bagkok samples could be detected. In view of this problem the results for cadmium do not appear to be very meaningful.

McKenzie and Neallie (1974) reported on hair cadmium values but concluded that hair cadmium levels are not useful in populations with low exposure, since no significant differences were found among the various study populations.

Rosmanith _et_ _al_. (1975, 1977) reported no significant findings for hair cadmium levels in their study of 413 children in a northern German industrial town.

In summary, assessment of cadmium levels in hair appears to be of questionable utility, unless used jointly with urine and blood cadmium determinations. Technical problems in collecting appropriate hair samples and in analytic techniques require further study. Also, the process of cadmium deposition in hair is not well understood.

3.3 RESULTS OF AUTOPSY STUDIES

Crucial to assessment of the effects of cadmium on human populations is the necessity of determining key organ levels of the metal and, where possible, total body burden. Generally it is not feasible to assess these levels in humans other than through autopsy studies, and a number of investigators have carried out such surveys of selected organ levels. These studies can be roughly classed into case studies concerned with specific diseases or population studies as discussed below. Before proceeding, it should be noted that some workers (Harvey _et_ _al_., 1975; 1979; Ellis et al., 1979)) have recently carried out _in_ _vivo_ neutron activation analysis studies of cadmium levels in organs of human volunteers. Such an approach, however, is still considered to be largely experimental and has only recently reached a stage of development whereby it has begun to be employed as a method for studying large populations.

It is necessary to point out some limitations of the data obtained from autopsy studies. The cases coming to autopsy do not really constitute a representative sample of a given population. The requirements for performing an autopsy vary from country to country, and different population segments differ significantly in their willingness to consent to autopsies not legally required. It is also well known that this attitude is related to social status, occupation, and housing, all of which are factors associated with different degrees of exposures to various toxins and pollutants and with nutritional and health status. The technical problems of speed, collection of information retrospectively, and the proportion of dead without living contacts all add to the difficulty of obtaining reliable data needed to analyze and interpret findings. Finally, there is the problem of defining "normal" or "healthy" individuals. Usually, accidental deaths are defined as "normal" or "healthy," but the quality of the examination of accident cases to determine this status may also vary.

Autopsy studies which report findings for unselected population groups and which are large enough to present cadmium concentrations further categorized by age give support to the findings from the earlier studies which show that cadmium concentrations in liver increase with age but may taper off after 60 or 70 years of age. Such studies also show that cadmium concentrations in the kidney, too, increase with age until about age 50 is reached; then there is a decrease. In addition to these age-related patterns of change in liver and kidney cadmium concentrations, smoking has been identified as being a key determinant of liver and kidney cadmium levels; that is, cadmium levels in liver and kidney are typically reported to be higher for smokers than non-smokers across all age categories.

Elinder et al. (1976) reported on 292 autopsies from Stockholm. The age distribution for the 292 cases is shown in Table 3-4, and the data reflect the above-noted age- and smoking-related patterns. This table also presents geometric means ($\bar{X}$) and standard deviations (SD). Figure 3-2 presents the findings for kidney cortex concentrations.

Table 3-4. CADMIUM IN HUMAN LIVER[a,b]
(μg/g wet weight)

		Age (yr)									
		0 - 9	10 - 19	20 - 29	30 - 39	40 - 49	50 - 59	60 - 69	70 - 79	80 - 89	90 - 99
All subjects	N	7	24	33	34	40	43	39	41	25	6
	$\bar{x}$	0.26	0.51	0.60	0.60	0.68	0.85	1.02	1.05	0.53	0.83
	SD	1.66	1.88	1.88	2.48	2.04	2.24	2.25	2.77	2.80	1.81
Males	N	5	18	19	22	24	21	19	20	14	3
	$\bar{x}$	0.33	0.55	0.58	0.51	0.62	0.77	0.84	0.96	0.59	0.53
	SD	1.54	1.82	1.98	2.80	2.01	2.56	2.26	2.91	2.21	1.23
Females	N	2	6	14	12	16	22	20	21	11	3
	$\bar{x}$	0.15	0.40	0.63	0.80	0.79	0.94	1.22	1.14	0.46	1.29
	SD	1.05	2.06	1.76	1.76	2.07	1.95	2.18	2.69	3.67	1.65
Nonsmokers	N	...	...	6	1	1	6	11	14	12	2
	$\bar{x}$	...	...	0.52	1.01	0.66	0.48	0.72	0.94	0.46	0.72
	SD	...	...	1.77	...	...	2.07	2.78	3.13	3.26	2.16
Smokers	N	...	...	7	10	13	15	15	13	1	1
	$\bar{x}$	...	...	0.77	0.57	0.77	1.14	1.24	1.32	0.89	2.17
	SD	...	...	1.55	2.63	2.01	2.72	2.14	2.58	...	...

[a] Mean ($\bar{X}$) and standard deviation (SD) are geometric. Tolerance intervals are calculated by multiplying or dividing $\bar{X}$ by SD.

[b] From Elinder *et al.*, 1976.

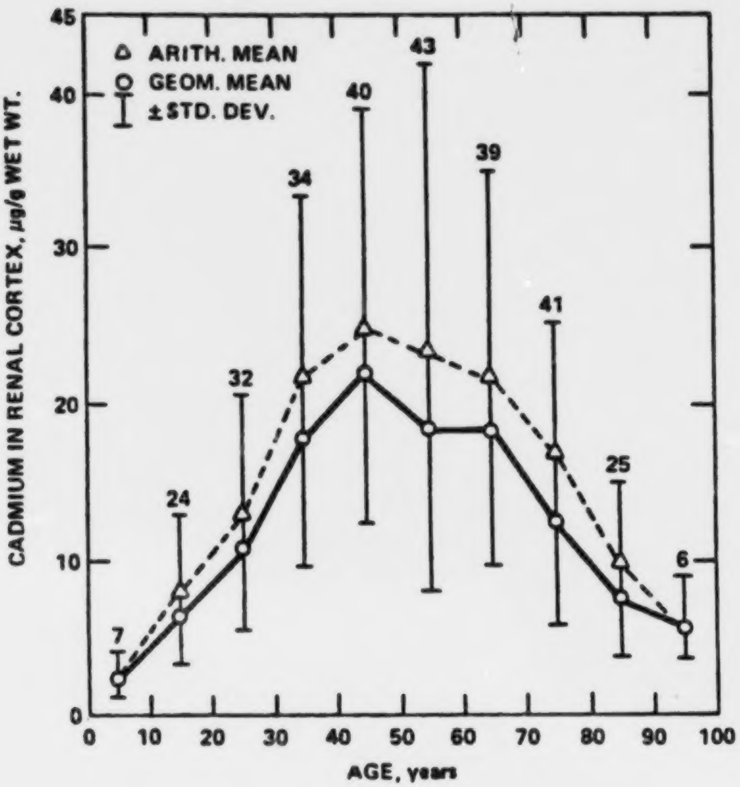

Figure 3-2. Geometric and arithmetic means of cadmium concentration in kidney cortex are shown for each decade of life.

Source: Elinder et al. (1976).

Tsuchiya _et_ _al_. (1976) reported on 106 autopsies for Tokyo residents dying of accidental causes. Table 3-5 presents the findings for renal cortex cadmium concentrations. The age-related pattern of change is clearly evident.

Miller _et_ _al_. (1976) in Australia found renal cadmium concentrations that followed the same age-associated pattern in 91 autopsies. Figure 3-3 presents their findings for mean cadmium concentrations in kidneys.

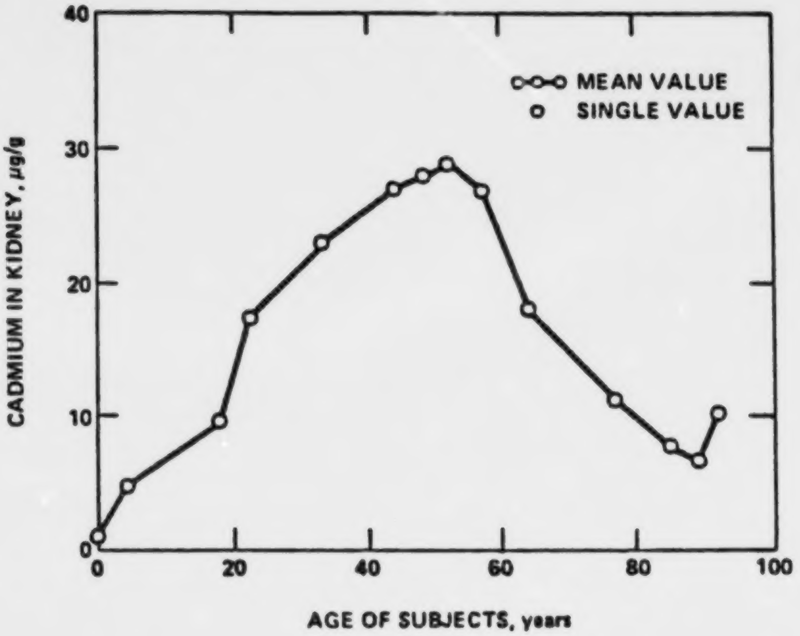

Figure 3-3. Cadmium in whole kidney tissues and its relationship to age.
Source: Miller et al. (1976).

Gross _et_ _al_. (1976) reported on a series of 106 autopsies, from Cincinnati, Ohio, and Table 3-6 shows the arithmetic mean ($\bar{X}$) and standard deviations (±SD) for age categories. The concentrations for liver increased until the sixth decade, when they appeared to level off. Cadmium concentrations for kidney increased until ages 45 to 54 and then showed a decrease.

Table 3-5. CADMIUM CONCENTRATION IN HUMAN RENAL CORTEX BY AGE: MEANS AND 99% LEVEL OF SIGNIFICANCE[a]
(μg/g)

Age	Mean	S.D.	99% Level of significance[b]	N
0 ~ 9	4.75	5.07	17.43	13
10 ~ 19	33.2	31.48	--	5
20 ~ 29	46.26	21.53	100.09	38
30 ~ 39	69.21	29.31	142.49	27
40 ~ 49	85.07	47.49	203.8	11
50 ~ 59	125.3	56.74	--	6
60 ~ 69	125.88	14.20	--	3
70 ~ 79	37.9	--	--	1
80 ~	94.68	18.7	--	2
Total	57.99	41.85	162.62	106

[a] From Tsuchiya _et_ _al_., 1976.

[b] $\bar{X}$ + (S.D. x 2.5)

Table 3-6. AGE GROUP MEANS AND STANDARD DEVIATIONS FOR TISSUE CADMIUM[a]
(ppm wet weight)

	Liver			Kidney		
Age group	N	$\bar{X}$[b]	±SD	N	$\bar{X}$	±SD[c]
Abortuses	19	0.01	0.00	19	0.07	0.06
0-1 mo	7	0.01	0.01	7	0.05	0.04
1-23 mo	9	0.05	0.05	9	0.13	0.09
2-5 yr	7	0.33	0.35	7	13.33	22.72
6-12 yr	4	0.66	0.49	4	6.23	6.71
13-18 yr	11	0.97	0.69	11	8.57	3.97
19-24 yr	10	0.82	0.54	10	13.73	6.99
25-34 yr	10	1.25	0.75	10	24.40	14.10
35-44 yr	6	0.88	0.66	6	29.62	14.97
45-54 yr	3	1.75	1.86	2	39.35	13.79
55-64 yr	9	1.96	1.30	9	30.09	17.22
65+ yr	10	1.97	1.08	10	20.89	12.26
Total	106	0.88	1.19	105	13.65	17.60

[a] Adapted from Gross _et_ _al_. (1976).
[b] Arithmetic mean.
[c] Standard deviation.

Syverson et al. (1976) in Bergen, Norway, examined liver and kidney cadmium concentrations in 76 autopsies. These authors also found the age-associated patterns for cadmium concentrations in liver and kidney. They reported data for urban and rural residence, and Table 3-7 presents these findings. Smoking status also showed higher values for cigarette smokers than for non-smokers, and blue-collar workers had higher concentrations than white-collar workers and "others," a group consisting mostly of housewives.

Vuori et al. (1979) in Helsinki, Finland, assessed cadmium levels in autopsy specimens of aorta, heart, kidney, liver, lung, pancreas, and skeletal muscle obtained from 86 humans who had died in traumatic accidents and who were verified, at autopsy, as not having suffered from any chronic diseases. The results of the study are summarized in Table 3-8, with cadmium levels observed for different tissues listed according to age group. The small number of females in most age categories precluded separate evaluation of cadmium levels by sex; the lack of information on the smoking habits of the subjects also precluded evaluation of the effects of smoking status.

In general, the Vuori et al. (1979) results indicate that the average cadmium tissue concentrations were highest in kidney, followed in decreasing order by: liver, pancreas, lung, aorta, heart and muscle. When the effect of age on the cadmium tissue levels reported for both sexes together is evaluated, the same age-related patterns as noted earlier tend to emerge. That is, the mean and median values for all tissues were universally low in the early years of life, but generally increased with age up to maximums reached at various points during adulthood and old age. Cadmium concentrations in muscle showed the best correlation with age ($N = 86$, $r = 404$, $p < 0.001$) over the entire age range studied; however, over the first 50 years of life, kidney cadmium concentrations were even better correlated

Table 3-7. MEAN CADMIUM VALUES RELATED TO PLACE OF RESIDENCE[a]

Residence	N	Age (year) Geometric Mean	Liver Cd (μg/g dry weight)		Renal cortex Cd (μg/g dry weight)		Renal medulla Cd (μg/g dry weight)	
			Mean	SD	Mean	SD	Mean	SD
Urban	52	65.9	8.1	± 5	101	± 60	62	± 42
Rural	24	51.0	8.1	± 5	98	± 50	54	± 30
Total	76	60.8	8.1	(1.1-24.3)[b]	100	(22-297)[b]	57	(6.7-171)[b]

[a] Adapted from Syversen _et_ _al_. (1976).

[b] Range.

Table 3-8. The average cadmium concentration in the tissues examined (geometric means and medians), the ranges and the number of samples above the detection limit/number of samples in each age group; both sexes are included, with total number of subjects for each age group indicated in parentheses.[a]

Tissue	Age group (years)							
	0-9 (N = 3)	10-19 (N = 16)	20-29 (N = 24)	30-39 (N = 12)	40-49 (N = 14)	50-59 (N = 7)	60-69 (N = 4)	≥ 70 (N = 6)
Aorta								
Mean	0[b]	0.05	0.20	0.53	0.41	0.50	1.03	0.15
Median	0	0.11	0.36	0.38	0.56	0.57	1.38	0.47
Minimum	0	0	0	0.17	0	0	0.20	0
Maximum	0.15	0.60	12.0	9.49	5.31	4.54	5.96	0.82
N	1/3	10/16	19/24	11/11	11/14	6/7	4/4	3/5
Heart								
Mean	0	0	0.05	0.06	0.09	0.06	0.22	0
Median	0	0	0.09	0.09	0.22	0.10	0.21	0
Minimum	0	0	0	0	0	0	0.14	0
Maximum	0.03	0.38	0.89	0.74	0.56	0.32	0.42	0.63
N	1/3	7/16	16/24	8/12	10/14	5/7	4/4	2/6
Kidney								
Mean	6.73	25.3	49.4	78.1	86.9	83.7	87.1	58.7
Median	15.8	24.9	54.9	74.5	99.3	78.7	100	76.2
Minimum	11.1	11.4	2.40	33.0	17.8	49.3	48.7	21.8
Maximum	17.4	44.6	197	150	239	178	123	143
N[c]	3/3	16/6	23/23	9/9	13/13	7/7	4/4	5/5
Liver								
Mean	0.25	2.41	3.06	2.69	3.72	2.39	4.47	3.38
Median	1.40	2.41	3.36	2.75	3.69	2.85	4.39	3.57
Minimum	0	1.24	0.57	0.38	0.97	0.12	3.09	0.54
Maximum	1.61	4.73	10.5	10.6	9.31	15.6	6.72	10.3
N	2.3	16/16	24/24	12/12	14/14	7/7	4/4	6/6
Lung								
Mean	0	0.27	0.66	1.35	0.67	0.73	0.87	0.03
Median	0	0.96	0.96	1.76	1.43	0.89	0.87	0
Minimum	0	0	0	0.07	0	0.21	0.53	0
Maximum	0.07	3.36	7.57	4.95	6.80	2.40	1.51	1.71
N	1/3	13/16	20/23	12/12	12/14	7/7	4/4	2/6
Muscle								
Mean	0	0	0.04	0.03	0.08	0.07	0.29	0.04
Median	0	0.03	0.07	0.06	0.18	0.11	0.29	0.08
Minimum	0	0	0	0	0	0	0.71	0
Maximum	0.03	0.22	0.39	0.17	0.29	0.48	0.50	0.47
N	1/3	9/16	16/24	7/12	10/14	5/7	4/4	3/6
Pancreas								
Mean	0.14	0.50	1.94	2.29	2.31	1.30	2.21	1.68
Median	0.47	0.83	1.90	2.23	3.05	0.64	2.31	1.44
Minimum	0	0	0.43	0.70	0.30	0.36	1.30	0.56
Maximum	0.85	1.89	10.3	9.71	9.08	8.13	3.41	3.46
N	2/3	14/16	23/23	12/12	14/14	7/7	4/4	5/5

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[a] From Vuori et al. (1979)

[b] 0 stands for "under the limit of detection," which was about 0.03 μg g dry weight.

[c] Due to an accident in a series of analyses, four results of cadmium in kidney are lacking.

with age ($N = 63$, $r = 0.580$, $p < 0.001$). Concentrations of cadmium in the different tissues were also found to be highly correlated with cadmium levels obtained for virtually all other tissues at comparable ages.

A further group of reports for autopsy studies did not present data for general populations with a wide distribution by age. The persons reported on either constituted a single age group or were selected to investigate the association of cadmium and specific diseases. Data concerned with "normal," "reference," or "control" groups has been selected from such studies for presentation.

Morgan (1970) in Birmingham, Alabama, studied cadmium concentrations for older males. The "normal" group's mean age was 61 years and included 55 persons. The mean and standard deviation for liver cadmium concentration was 182 ± 99 μg/g ash and 2406 ± 1299 μg/g ash for kidney cadmium concentrations.

Ostergaard et al. (1977b) presented data for 61 cases where cigarette smoking status was known. Non-smokers ($N = 19$) showed the following for whole kidney μg/g ash: Arithmetic mean (and range): 1106 (347 to 2466) μg/g ash, and a geometric mean of 953. The 42 smokers showed the following: for those with less than 20 cigarettes per day ($N = 11$), arithmetic mean (and range): 2415 (947 to 3821) μg/g ash and geometric mean of 2242 μg/g ash; for heavy smokers ($N = 12$) using 20 or more cigarettes per day: arithmetic mean (and range); 2778 (961 to 7493) μg/g ash and geometric mean of 2310 μg/g ash.

Lewis et al. (1972) in Boston, Massachusetts, examined liver and kidney tissue from 172 cadavers. The 161 males had a mean age of 61 ± 1.0 yr, and the mean age of the 11 females was 70 ± 3.1 yr. Total mean cadmium content for kidney (N = 171) was 9.06 ± 0.50 mg and that for liver (N = 172) was 2.92 ± 0.14 mg. When these findings were examined for the effect of smoking, differences for smokers and non-smokers were found as follows: Non-smokers (N = 34) had a mean of 4.16 ± 0.51 mg for kidney, smokers (N = 138) 10.28 ± 0.57 mg. Means for liver were: non-smokers 2.28 ± 0.25 mg, smokers 3.06 ± 0.16 mg.

Kidney cadmium levels for non-smokers and smokers were measured by Johnson et al. (1977). Cadmium levels were significantly greater ($p < 0.001$) for smokers, the difference between the two groups being 6.9 μg/g average concentration.

In summary, highly consistent patterns of results have emerged from the autopsy studies reviewed above, with age-related and smoking-related changes in human liver and kidney cadmium concentrations being among the more salient features of the data base. It is clear, for example, that cadmium is typically present in liver at very low levels (<0.5 μg/g) during the first decade of life but gradually accumulates in that organ until the late decades of life, reaching mean maximum concentrations of ca. 1-2 μg/g for non-smokers at age 50 and beyond. For smokers the observed liver concentrations at various ages are usually approximately double those of non-smokers. It is interesting that one recently reported study on in-vivo neutron activation analysis yielded an estimate of 2.2 ± 2.0 ppm (mean ± S.D.) liver cadmium concentration in 10 adult control subjects compared against 11.0 ± 2.0 ppm values observed for 21 adults aged 40 to 62 years (mean 53) living in an area of high cadmium soil contamination (Harvey et al., 1979). Also of interest are the results of another neutron activation study of liver cadmium concentrations in normal adult male volunteers, in which liver cadmium levels of 2.3 ± 1.6 μg/g (mean ± S.D.) were observed for non-smokers and 4.1 ± 1.6 ppm for smokers. these values comport well with those derived from the autopsy studies.

Cadmium levels in human kidney, like those in liver are also normally very low during the first decade of life, steadily increase over the ensuing 4 to 5 decades, but reach maximum peak concentrations around age 50 before declining somewhat thereafter. Variations in cadmium concentrations in kidney cortex are of most interest, in view of subsequent discussions below of cadmium - induced renal dysfunction as a key human health effect associated with the accumulation of cadmium in kidney cortex. Of particular concern are concentrations that reach certain critical values (ca. 200 μg/g wet weight) in kidney cortex associated with the disruption of normal renal function. Summarized in Table 3-9 are estimates of kidney cortex cadmium levels for the U.S. adult population, as determined by autopsy studies listed in the table.

TABLE 3-9. CADMIUM IN THE KIDNEY CORTEX OF U.S. ADULT POPULATION
(μg/g wet weight)

Reference	Age	N	Mean	Standard Deviation	Range
Tipton and Cook, 1963	Adults	145	35	16	6-88
Indraparasit et al., 1974	31-80	134	22	14	
Gross et al., 1976	39-85	28	30		7-101
Johnson et al., 1977	40-59	59	26	8	4-109
Hammer et al., 1973	40-79	58	29		6-83
Morgan, 1972	62 mean	100	33		1-128

3.4 EPIDEMIOLOGICAL STUDIES OF CADMIUM EXPOSURE IN JAPAN

A number of comments appear in the preceding Health Effects sections dealing with the pathophysiological features of cadmium as they have been unveiled over the last two decades in cadmium-polluted areas of Japan, with emphasis on the most serious aspect of population response, Itai-Itai or "Ouch-Ouch" disease. A number of studies have also focussed on areas of cadmium pollution in Japan other than the Jintsu River basin, or Itai-Itai belt. Revelant Japanese epidemiological data will, therefore, be considered in two sections - one on Itai-Itai disease studies and another on other studies of cadmium pollution in Japan.

Some general comments, as follow, are in order with reference to the nature of the Japanese epidemiological studies which have been carried out so far.

(1) Different investigators have employed various techniques to assess the indicators of adverse health effects in these population groups under study. Until recently, when attempts were made in Japan to standardize the way in which one assesses cadmium-associated proteinuria, which is the most common indicator of chronic cadmium exposure, the methods for increased protein excretion were rather crude, semi-quantitative, and nonspecific. Thus, it is not always possible to compare these types of data gathered by different investigators; Friberg et al. (1974) discuss this difficulty in some detail.

(2) Questions arise in a number of cases as to the appropriateness of the control population groups taken for study with particular reference to close matching for age, diet, and nutritional status. For example, it is not clear that some study groups selected to control for dietary cadmium intake actually constitute true non-polluted diet groups.

(3) Given the retrospective nature of many of the studies, difficulty arises in attempting to draw correlations between factors such as diet and the present health status of the various exposure groups. For example, the exposure

in many cases has occurred over a number of years, several decades in some instances, while assessment of dietary cadmium is based on data collected much later, after the onset of overt effects. Ideally, one would like to have had a time-concordant profile of changes in dietary cadmium, if any, over this period.

(4) One can also argue that Japan constitutes a unique cadmium-exposure situation owing to heavy population density, the very close proximity of industrial to agricultural and other human activities, the geochemical nature of the ores mined and processed as to cadmium content, unique nutritional status of the affected populations, etc.; so its experience with cadmium may, therefore, not be applicable to the United States. As noted earlier, however, the collective Japanese experience with cadmium does appear to constitute a classic case of pollution in a heavily industrialized society which persisted for a number of years, with resulting effects remaining unidentified and unsuccessfully treated over quite some time.

3.4.1 Itai-Itai Disease Studies

The chronology of the development of Itai-Itai disease and the studies directed thereto have been extensively considered elsewhere (Friberg et al., 1974; Fulkerson and Goeller, 1973; Tsuchiya, 1978). These earlier literature evaluations will not, therefore, be repeated here; but rather some of the more recent data will be considered.

In Friberg et al. (1974) a good case was made for the etiological role of cadmium in the development of Itai-Itai disease, characterized by marked tubular proteinuria with osteomalacia and severe osteoporosis afflicting older females ($\geq$40 yrs) in the Fuchu area of Toyama Prefecture. As noted elsewhere in this report, however, the victims also had histories of marked nutritional deficiencies, a fact which has contributed to difficulty in defining the relative importance of the nutritional deficits versus cadmium as key etiological factors underlying the disease.

Nevertheless, in Cadmium in the Environment III (Friberg et al., 1975), additional studies from the Itai-Itai region of Japan were discussed as data supporting a likely connection between cadmium and various aspects of the Itai-Itai disease.

Shiroishi and Yoshida (9172), for example, selected a group of 123 men and 119 women over 40 years of age in S-village in the Fuchu area as an exposure group as used 75 men and 86 women in a different area as a control group. In their study, the prevalence of proteinuria among the exposed subjects increased from about 10 percent in the 40- to 50-year-age group to about 50 percent in the 70- to 80-year-age group. Proteinuria was assessed using the Kingsbury-Clark method as well as disc electrophoresis, while test-tape and OTB methods were employed for gulcosuria.

Also, the study of Fukuyama et al. (1972), the time of residence in the Fuchu area was correlated with cadmium excretion and renal dysfunction. Cadmium excretion was seen to reach a maximum at 40 years of living in the area, and after 45 years, almost all of the individuals showed renal dysfunction.

In the dietary study of Fukushima et al. (1973), an effort was made to correlate proteinuria and glucosuria in Fuchu area villages with cadmium levels in the rice (particulary non-glutinous rice) consumed in the villages studied. In 37 villages studied, renal deficit response rates (proteinuria and glucosuria) were seen to increase with increasing cadmium levels in rice, a significant correlation coefficient of 0.62 being obtained. Additional analyses confirming clear-cut associations between renal dysfunction response rates and cadmium levels in rice among inhabitants of the Jinzu River basin are presented by Nogawa and Ishizaki (1979).

It should be noted that earlier studies of existing proteinuria in Itai-Itai patients and other subjects from the Fuchu area involved rather nonspecific (Friberg, et al., 1974) total protein methods. More recently, however, attention has focused on the levels of specific types of urinary proteins which may be more pathognomonic for renal effects of cadmium.

One argument which has been advanced in defense of the notion that Itai-Itai disease is not cadmium-related is the fact that Itai-Itai disease appears to be confined to the Jintsu River basin, although a number of other cadmium-polluted areas exist in Japan. In 1975, however, Nogawa et al. claimed to have identified five cases of Itai-Itai disease among women in the Ichi River basin. All of these patients showed biochemical and other clinical evidence for the renal and bone damage sequelae associated with the malady. Autopsy data in one case were also consistent with the earlier data from the Jintsu River basin. Furthermore, the favorable response of three of these subjects to large doses of Vitamin D therapy parallels that seen in other victims of the disease.

Other factors have also likely contributed to the failure to find more conclusing evidence of Itai-Itai disease in other areas of Japan. In viewing the data available on Itai-Itai disease, for example, one is struck by the fact that in many early epidemiology studies on the subjects, investigators restricted themselves to the extreme clinical phase of the continuum of changes accompanying chronic cadmium exposure. Fortunately, this problem has since begun to be assessed more comprehensively and uniformly, taking into account the earliest signs of renal deficits of the type associated with manifestation of more severe aspects of Itai-Itai disease. Still, even after a large number of epidemiologic studies and health surveys in cadmium-polluted areas, the etiology of Itai-Itai disease is not yet completely clear. The disease was at first diagnosed as a vitamin-D resistant osteomalasia, but, based on studies of the type reviewed here, cadmium has been implicated as a likely factor contributing to the development of the disease. Importantly, however, malnutrition and other environmental factors may have promoted the toxic effects of cadmium in Itai-Itai patients.

Before discussing studies of other cadmium polluted areas of Japan, it should be noted that chromosomal aberrations occur in individuals with Itai-Itai disease as discussed in part in the Sub-Cellular Effects section (vide supra) of Chapter 2 and Section 3.8 of the present chapter.

3.4.2. Epidemiological Studies of Other Cadmium-Polluted Areas in Japan

Japanese areas besides the Fuchu region of Toyama Prefecture, where epidemiological studies have also been carried out include Ikuno, Tsushima, Kakehoshi, Bandai, Annaka, Omuta, and Uguisuzawa; and a review of these data was presented by (Friberg et al., (1974).

In a more recent rather detailed report, Kjellström (1976) has reviewed and critiqued data from these areas of cadmium exposure in Japan where systemic effects such as proteinuria have been considered from the standpoint of dose-effect/dose-response relationships of cadmium.

The extent to which data comparisons can be made is restricted somewhat by the fact that proteinuria has been assessed in different ways, and not all factors have been matched in selecting control groups.

In 1972, a study was carried out involving 1560 individuals from the Ichi River basin in Hyogo Prefecture, an area where the likelihood of pollution extends back for several centuries. Three control-area groups of 1574, 2002, and 638 persons were also employed (Watanabe et al., 1973). The corresponding proteinuria prevalence rates (determined by the sulfo salicyclic acid method) were 58, 33, 4, and 9 percent, respectively. Differences in these groups may be confounded by the fact that not all control areas used the same protein analysis technique. In a later study, Watanabe and Murayama (1974) found elevated β_2-microglobulin and lysozyme in urines of individuals from the most heavily exposed group (H area). It was in this same area that Nogawa et al. (1975) later reported five cases of Itai-Itai disease (vide supra).

Another zinc mine which was probably a long-term pollution source spanning several centuries appears to have contributed to the occurrence of significantly increased proteinuria in the Tsushima area of Nagasaki prefecture, as discussed by Friberg et al., (1974).

In the four villages of the Kakehoshi area in Ishikawa prefecture where cadmium pollution occurred from two long-active copper mines, a study of Ishizaki (1972) turned up proteinuria prevalence ranging from 39 percent for the worst exposure to 30, 28, and 22 percent for the others. No control group was employed in this study.

Japanese population groups in the areas of zinc smelters have also been studied. In the Bandai area of Fukushima Prefecture, the site of a zinc smelter, a study (Fukushima Prefecture, 1971) of 1324 men and women over 30 years of age in the pollution belt, and using 215 women in a control area, indicated that the prevalence of proteinuria was 12.3 percent in the polluted area compared to 4.7 percent in the control area.

Another site for a zinc smelter is the Annaka area of Gumma prefecture. A study of 2397 persons (men and women, more than 30 years of age) in the polluted area around the smelter showed a prevalence of proteinuria (12.1 percent), but this was not significantly different from the rate observed for a group of 895 control subjects (Kakinuma et al., 1971), as described in Friberg et al. (1974). These findings have later been ascribed to the brevity of the significant exposure period, which occurred mainly only over the last decade (Kjellström, 1976).

The most recent study of the prevalence of proteinuria in a zinc-smelter area in the Omuta region (Friberg et al., 1974) showed a rate of 18.2 percent for the polluted area versus a rate of 6.8 percent for control subjects.

Saito et al. (1977) carried out a detailed study of proteinuria in the Hosogae area of Akita prefecture which is adjacent to a major copper refinery operating for the past century, these studies spanning 1972 to 1975. These workers found that 13 to 22 percent of the area's population over 35 years old had proteinuria and glucosuria versus the general occurrence of 20 percent in all of Japan. Also, the levels of urinary β_2-microglobulin in this group increased with age and length of residence in this area.

Extensive soil contamination and a high contamination of rice are present in this area. In the studies of Watanabe et al. (1973), noted above in connection with proteinurea, urinary cadmium levels were related to the village average rice cadmium levels; adults excreted ca. 7 µg cadmium/ liter at rice levels of 0.4 µg/g and this value rose to ca. 14 µg/liter at 1.1 µg/g in rice. These values correspond to 240 and 660 µg daily of cadmium intake. Kjellström (1977) found that women aged 50-59 and having long-term cadmium intake had blood levels of ca. 3 µg/dl and 24 hour urinary excretion levels of ca. 15 µg. These latter values can be compared to calculated estimates, based on a 600 µg cadmium intake value, of 3.4 µg/dl blood and 14 µg/24 hour urine respectively (Kjellström and Nordberg, 1978).

3.5 EPIDEMIOLOGY OF CADMIUM, HYPERTENSION, AND CARDIOVASCULAR DISEASES

Hammer et al. (1972) a reviewed information an the relationship between cadmium and hypertension and also presented data to support some of their criticisms of the approaches taken by earlier investigators. Essentially they questioned the "single cause" approach pointing out that, particularly for conditions of high prevalence, this approach has inevitably failed. Much of the more recent work has proven them right in this contention. Investigators who have controlled for smoking status have found that the association of higher cadmium concentrations and hypertension is not independent of smoking status.

Thind et al. (1976) and Glauser et al. (1976) found significantly higher cadmium concentrations in blood of hypertensive patients than in normotensive controls, but neither of these groups of investigators controlled for smoking status. Beevers et al. (1976a) found not only no difference for cadmium concentrations for hypertensives and normotensives but instead did find that smokers and non-smokers, regardless of pressure, showed differences in cadmium concentrations. A further report from this team (Beevers et al., 1976b) indicates that higher concentrations of lead were found in blood of male hypertensives than that of male normotensives. A difference in the same direction but not statistically significant was found for female patients and controls. These subjects came from the same area and clinic as those examined in the earlier study. The authors concluded that the findings of an association of hypertension and blood lead concentration is due to the quality of the tap water since this area has high lead levels in its drinking water. The case for an association for cadmium and hypertension appears weakened by this finding.

Autopsy studies were conducted by Ostergaard (1977a,b) and by Syverson *et al*. (1976). These investigators controlled for smoking and found no differences, Ostergaard (1977a,b) reporting higher levels among normotensives who smoked than among hypertensives. The reports from the North Carolina study (Shuman *et al*., 1974; Voors and Shuman, 1975) did not adequately control for smoking. They found a statistically significant association for zinc concentrations in kidney tissue, and an association, consequently, for zinc-cadmium ratio, but not for cadmium concentrations *per se*.

The association between hypertension and hard water and associated levels of cadmium in water has been discussed by Perry *et al*. (1974). There is no firm evidence as to the significance of this variable. Rather, the currently available data are not definitive and can best be characterized as inconclusive and requiring further research.

Early studies by Hunt *et al*. (1971) and Hickey *et al*. (1967) related mortality rates to air cadmium levels. These statistical approaches use total mortality experience without taking into account population characteristics such as age distributions. Further, they do not take into account the fact that cadmium in air is not so ubiquitous as other pollutants, and single measures for air concentrations for entire populations are of dubious value.

Bierenbaum *et al*. (1975a,b) analyzed cardiovascular/renal mortality in populations with hard and soft water as well as different levels of cadmium concentrations in water using the Missouri and Kansas populations of the Kansas City metropolitan area. The investigators found higher mortality for the hard-water area of Kansas than Missouri. Two matched groups of 260 adult volunteers, one each from the two areas, were examined for blood pressure, electrocardiographic findings, selected serum-lipids, uric acid, and angina.

Some statistical differences for the two groups were found, but smoking status was not controlled for. The significance of their finding has been questioned (Sharret and Feinlieb, 1975).

Autopsy studies reported by Voors et al. (1975) and Shuman et al. (1974) found an association between cadmium concentration in liver and death from heart disease. Syverson et al. (1976), however, found neither an association for cardiovascular disease nor for hypertension, as discussed above.

The evidence for an association between cadmium and cardiovascular disease is, therefore, no clearer than that for hypertension. The groups studied are either extremely small or, if larger, were not controlled for relevant factors. It is therefore, impossible at this time either to rule out the postulated relationship or to confirm it.

3.6 EPIDEMIOLOGICAL STUDIES OF THE RESPIRATORY TRACT

Studies concerning cadmium-induced effects on the lungs, other than cancer, almost universally concern occupationally exposed workers and have already been discussed above in Chapter 2 (Health Effects). Briefly, Lauwerys et al. (1974), Scott et al. (1976), and Smith et al. (1976a) found decreased pulmonary function in workers exposed to high air cadmium concentrations for long periods. Scott et al. (1976) also reported "restrictive airway disease" to be prevalent to a greater degree in the most exposed group.

Smith et al. (1976a) found mild and moderate interstitial fibrosis in an occupational study group with a history of high exposure to airborne cadmium (i.e. levels $>0.2\ mg/m^3$). Associated impairments in pulmonary function, as indexed by significantly decreased forced vital capacity (FVC) were also observed in relation to data obtained for low exposure co-workers and unexposed control subjects matched for age smoking status, and other pertinent characteristics. A clear dose-response relationship was observed between forced vital capacity and both average urinary cadmium concentration ($r = 0.53$; $P < .003$) and maximum urinary cadmium concentration ($r -.51$; $P < 0.05$). Linear regression analyses further indicated that decreases of 2.8% in predicted FVC occur as average urinary cadmium excretion levels increase by 10 μg/l cadmium as a single etiological factor. The cadmium/zinc ratio was not determined.

Morgan _et_ _al_. (1971) compared the tissue cadmium concentrations of autopsied patients grouped by cause of death. Cadmium concentration in liver was significantly higher in the group with the diagnosis of emphysema. A second group with a combined diagnosis of cancer of the lung and emphysema showed significantly higher cadmium concentrations for both liver and kidney. Smoking was not controlled for even though the investigators attempted to collect this information. Occupational exposure was reported for 23 percent of the "emphysema only" group, but only 4 and 5 percent of the "lung cancer" and "emphysema and lung cancer" groups had such exposures. These authors stressed that the findings are only suggestive. Similar distributions of mean values for zinc concentrations in liver and kidney suggest that it is not possible, based on these study results, to implicate cadmium as the key etiological factor associated with the occurence of lung cancer cases studied.

While there is no question that occupational exposure at high levels produces decreased pulmonary function, restrictive airway disease, interstitial fibrosis, and emphysema, no good evidence exists at present as to the effects of gradients of exposure levels for "normal" populations without high levels of occupational exposure.

3.7 CADMIUM AND CANCER

The investigations of causes of death among workers are one source of data; studies of tissue concentrations by cause of death are another source. The data are sparse and subject to the limitations of retrospective study design and autopsy studies.

Potts (1965) conducted a health survey in an English alkaline-battery factory where source data for cadmium concentrations in air was available. The plant had been in operation for over 40 years, and the health status of past and present workers was assessed. There were 74 workers who had had exposures of more than 10 years, and 8 of these had died. Among these deaths, five were from cancer; and three of these were cancer of the prostate. These eight had worked at the plant when exposure levels had been high and before moving into a new building where air levels were much improved and where measures continued to be taken to achieve further reductions. Potts' report did not give enough information to interpret his striking finding in relation to mortality in the general population, and he presented no data for causes of deaths among workers with less than ten years' exposure. Also not clear is the reliability of establishing the base of 74 workers with ten or more years of exposure.

Kipling and Waterhouse (1967) reported a further study of the workers in this battery plant. They had extended the search for causes of death to all those with at least one year's exposure. They found 248 workers with this exposure with a total of 12 deaths from cancer in this group. Among these 12, four were cancer of the prostate. (Three among these were also included in Potts' findings). Mortality experience in an unidentified population stated to be similar was used to calculate expected numbers of deaths for all cancers and for specific cancer sites. For the four cancer sites, and for cancers for all sites, significant differences between observed and expected numbers of deaths were found only for cancer of the prostate.

The next relevant study of occupationally exposed workers was reported for workers at a cadmium smelter in the United States. Lemen et al. (1976)

used employment histories to establish a population of 292 workers with more than two years' exposure which were a cohort for employment during a 30-year employment period between January, 1940, and December, 1969. Very thorough investigation produced information on vital status. It was found that, by 1974, 92 had died, 180 were known to be alive, and 20 were lost to observation. Causes of death were established and standardized mortality ratios (SMR) were calculated so that excessive risk could be analyzed. Mortality from cancer at all sites was found to exceed the expected number of cancer deaths by a statistically significant margin. Among the deaths from cancer, 12 were from sites in the respiratory system; and this observed number also gave a significant excess with an SMR of 235. Cancer of the prostate was also found to have a significantly increased risk among these workers. The latency period for prostatic cancer deaths found both by Potts (1965) and Kipling and Waterhouse (1967) is 20 years or more. Lemen _et_ _al_. (1976) found the same latency period. It should be kept in mind that the Lemen _et_ _al_. (1976) study did not control for smoking.

A study of mortality among rubber workers was conducted by McMichael _et_ _al_. (1976). This study was not confined to workers exposed to cadmium alone, and it is therefore not possible to implicate cadmium specifically in the mortality from cancers that was found. Cancer of the prostate showed an SMR of 119, which was only slightly elevated. A more detailed analysis of the specific jobs of these prostatic cancer deaths showed that workers in compounding and mixing areas and maintenance workers had a higher risk for this cancer. No air cadmium levels at the various worksites were determined. These specific mixing jobs expose workers to cadmium and other metal oxides.

Autopsy studies have compared cadmium concentrations in tissues by causes of death. Lewis et al. (1972) found in their 172 autopsies that higher concentrations of cadmium in kidney cortex, liver, and lungs were found in cases of death from cancer of the bronchus and lungs. However, when cigarette smoking is controlled for, these differences disappear. This forces reconsideration of the findings reported earlier by Morgan et al. (1970, 1971), who found significantly higher cadmium tissue content for causes of death from cancer of the lung but did not control for smoking status. Voors et al. (1975) reported on their autopsy series that they found no association between higher cadmium tissue concentrations and deaths from cancer.

Kolonel (1976) reported on a survey of patients at Roswell Park Memorial Institute for an 8-yr period, 1957 to 1964. All white males aged 50 to 79 yr with a diagnosis of renal cancer were compared to two control groups: one of all comparable males with non-malignant diagnoses and the second of males with cancer of the colon. From the smoking and employment histories all subjects were categorized as "exposed" or "not exposed" via the respiratory route. Data from the dietary history were used to categorize the men as nutritionally "exposed" or not. Two sources of respiratory exposure and the dietary exposure were therefore considered. Relative risk for cancer of the kidney was increased only when smoking and occupation were considered together, in which case the age-specific, relative risk was 4.4, whereas for smoking alone, the relative risk was 1.2.

There is evidence in the literature which suggests that cadmium may be a factor in the etiology of cancers at various sites, but the association with cadmium is not firmly established. For example, Lemen et al. (1976) reported statistically significant increases in bronchogenic cancer to be associated with cadmium exposure, but did not control for smoking. Also, for lung cancer, an association was found by Morgan (1970, 1971) but not by Voors et al. (1975) or

Lewis et al. (1972) when cigarette smoking was taken into account in the latter study. Prostate cancer was reported in several studies to be associated with occupational exposure to mixtures of airborne particulate matter which contained cadmium oxide as a common component. Although the evidence is not conclusive, the possibility that cadmium can cause cancer cannot be dismissed. Both the U.S. Environmental Protection Agency's Carcinogen Assessment Group (1978), and the WHO International Agency for Research on Cancer (IARC) monographs 11 and 20 (1976) reached the same conclusion in regard to occupational exposure and cancer risks.

3.8 EPIDEMIOLOGICAL STUDIES RELATING TO CHROMOSOMAL ABNORMALITIES

A number of studies addressing the question of chromosomal abnormalities in humans and involving various exposure conditions have been reported. Shiraishi (1975) pointed out the occurrence of a number of chromosomal abnormal ities in patients with Itai-Itai disease. Other studies touching on this issue are considred here.

In a study that also included Itai-Itai patients, Bui et al. (1975) analyzed lymphocyte cultures from six female Itai-Itai patients, four control Japanese samples, five cadmium-exposed Swedish workmen, and three Swedish controls and were unable to see any significant differences within either of the two sets of groups. Interestingly, however, the Swedish groups showed a lower frequency of abnormal cells than either of the Japanese groups. It is unlikely that the greater time lag from collection to culture in the case of the Japanese samples (4 days) could constitute an artifact in these results, since these investigators had not experienced any time-dependent effect of culturing of this magnitude (4 days) in the past.

In the occupational exposure studies of DeKnudt and Leonard (1975) and Bauchinger et al. (1976), significant chromosomal abnormalities were observed. In the former study, where workmen were exposed to cadmium and lead via dust and fumes, yields of chromatid exchange, spiralization disturbance, chromosome translocation, and ring and dicentric chromosomes obtained were higher than in a group of control, low-cadmium-exposure workmen. In the latter data (Bauchinger et al., 1976), chromosomal damage was mainly of the chromatid type. Confounding these results, of course, is the fact that lead exposure had also occurred, thus this toxin could not be ruled out as being the main factor or a cofactor operating synergistically with cadmium.

All of the various studies, considered collectively, indicate that the issue of cadmium as the etiological factor in chromosomal abnormalities is still open to controversy.

3.9 EPIDEMIOLOGICAL STUDIES OF OCCUPATIONAL EXPOSURE TO CADMIUM

A comprehensive review of all of the studies of occupational groups regarding the health effects of cadmium exposure is outside the purpose of this report. Where specific studies have been deemed appropriate to demonstrate the magnitude of cadmium's health effects in man, these data have been incorporated into the appropriate sub-sections of the Health Effects report.

For a more appropriate compendium in which occupational exposure is the chief emphasis, one is directed to the recent National Institute of Occupational Safety and Health's Criteria Document for Cadmium (NIOSH, 1976).

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4. HUMAN HEALTH RISK ASSESSMENT OF CADMIUM

4.1 INTRODUCTION

In several respects, cadmium is rather unique among those metallic elements that are toxic to man. Its very long biological half-life leads to a steady increase in body burden over an individual's lifetime. Unlike lead, however, cadmium accumulates in soft tissue, chiefly the kidney, and little of the body burden is deposited in bone where it might become inert. Furthermore, there is no treatment available to prevent the accumulation of cadmium in the kidney or to remove or eliminate cadmium stored in the kidney or other soft tissues. Also, the adverse physiological effects associated with cadmium are essentially irreversible in nature. Thus, the most effective approach in protecting against its toxicity appears to be minimization of exposure to the metal. These two factors provide a strong basis for advocating limitation of human exposure in order to forestall adverse effects that may not appear until late in an individual's lifespan.

In addition to the above points concerning cadmium, e.g., its insidious gradual tissue accumulation over long periods of time, it should be noted that, so far as can be discerned to date, cadmium possesses no particular physiological benefit for man. Thus, there is no health-risk/health-benefit balance to be considered in discussing the hazards to public health associated with environmental exposure to the element.

To assess the issue of risk to public health posed by cadmium exposure, two aspects of the problem must be considered: (1) sources and levels of exposure and (2) population response.

Key questions about the sources of exposure that must be considered include: (1) What are the environmental sources of cadmium exposure of present or potential future concern in the United States? (2) What are the various routes by which cadmium enters the body? The latter question is a particularly vexing one in the case of a multi-media contaminant such as cadmium. A primary route of entry into the environment can lead to secondary and tertiary contamination; e.g., airborne cadmium contributes via fallout to soil levels which in turn influence the levels of cadmium in plants, animals, and food.

Several crucial questions must be considered with respect to population response:

(1) What are the human biological and pathophysiological responses to cadmium observed at environmentally relevant cadmium exposure levels?

(2) Do there exist within the general population in the United States or elsewhere certain sub-groups at particular risk to the adverse health effects of cadmium, either by reason of a special exposure relationship or an abnormally vulnerable physiological status?

(3) Quantitatively, what is the magnitude of the risk in terms of numbers of individuals potentially exposed to levels of cadmium sufficient to induce particular adverse health effects?

The first question posed was partially answered in the previous sections on health effects of cadmium (Chapters 2 and 3). It requires expansion here, however, to more fully consider dose-effect and dose-response relationships for humans and to assess the utility of various indicators of exposure in evaluating the effects of different types of exposure.

To better understand this portion of the present document, it would be helpful to define the various terms which will be encountered. "Dose" is the amount or concentration of a substance which is presented over time to the specific, intracellular site where the effect is imparted. Since it is not usually possible to assess directly the quantity of that substance in the living organism at the affected site ("effect site"), the external and internal doses are considered as indices mirroring the effect-site concentration. "External dose" is the amount of the toxic substance in the external environment (air, water, food, etc.) to which an organism is exposed. "Internal dose" is the absorbed portion of the substance and is an integrated reflection of all contributing external exposures.

"Effect" is a biological change resulting from exposure to a toxic substance. "Dose-effect relationship" is a quantitative relationship between the dose and a specific effect i.e., it reflects changes in the intensity of an effect as a function of variations in dose. Dose-effect relationships vary among members of a population, and the frequency at which this occurs is expressed as the dose-response relationship. "Response" specifically is defined by Nordberg (1976) as that proportion or percentage of a population that exhibits a specific effect at a given internal dose level.

Nordberg (1976) has defined the concept of critical organ, critical concentration in the critical organ, and critical effect. "Critical organ" is defined as that organ which first attains the critical concentration of a metal under defined situations and for a given population. The "critical concentration" is defined as the mean concentration of the toxic substance in the critical organ at which adverse functional changes appear. The "critical effect" is the first adverse effect that occurs along the continuum of dose-effect relationships.

4.2 EXPOSURE ASPECTS

Cadmium, although a relatively rare metal, is widely distributed naturally in the Earth's crust, often in close association with zinc and other metals. It is, therefore, rather ubiquitously encountered in trace amounts as a geochemical component of many surface soils, in underground water tables, and in surface waterways. Substantial additional amounts of cadmium, however, are continuously added to the "natural" background levels of the element in soils and water as a consequence of anthropogenic activities. Thus, in industrialized societies such as the United States, considerable amounts of cadmium enter the environment as a result of the manufacture, use, or disposal of cadmium-containing products or waste materials. Since little or no recycling of cadmium occurs, its use is said to be dissipative, i.e., the amount entering the environment roughly equals the amount produced or used; and this steady accumulation in the environment is one factor of considerable concern in assessing the risk associated with cadmium exposure.

The current amount of cadmium entering the environment annually in the United States is variably estimated at about 2,000 to 5,000 tons, with the lower figure being based on limited measurements and estimates for 1974 (Sargent and Metz, 1975; Yost *et al*., 1975) and the higher figure being the most recent data available to the United States Environmental Protection Agency (U.S. EPA, Sources of Atmospheric Cadmium, 1978). The latter figure may be higher because its calculation involved the use of stack-test data rather than mass balances. Of these amounts, about 20 percent arose from zinc mining and smelting, 30 percent from industrial use of cadmium, and the rest from inadvertent sources, i.e., from municipal incineration of waste materials, fossil-fuel use, phosphate fertilizer use, and sewage-sludge disposal. Cadmium released into the environment through such activities can eventually affect humans via contamination of air, water, or soil. Of particular concern is the entry of cadmium from any of these media, into the human food chain, as illustrated in Figure 4.1, and any consequent increase in exposure of humans to the metal.

Concisely discussed below are estimates of present cadmium levels encountered in air, water, soil, and food in the United States, along with major sources of cadmium contributing to existing levels of the metal in each of those media. Also discussed below are certain trends or factors that can be reasonably well discerned at this time as being potential future problems in terms of possibly contributing to increased cadmium exposures of human populations in the United States.

4.2.1 Ambient-Air levels of Cadmium

Widely varying amounts of cadmium have been detected in air over rural and urban areas around the world, with specific concentrations depending mainly on the degree of industrialization of a given region. In regard to natural background levels of cadmium in the ambient air, levels of atmospheric cadmium over remote rural areas and many small urban areas are usually very low and are often non-detectable. For example, numerous air sampling stations in small towns yielded frequent readings of 0.1 ng/m^3 or non-detectable values for cadmium in the air, as reported as part of the SAROAD data file, which compiles atmospheric data submitted by states (see EPA Multimedia Levels Cadmium, 1977, pp. 2-6 to 2-11). Thus, natural background levels

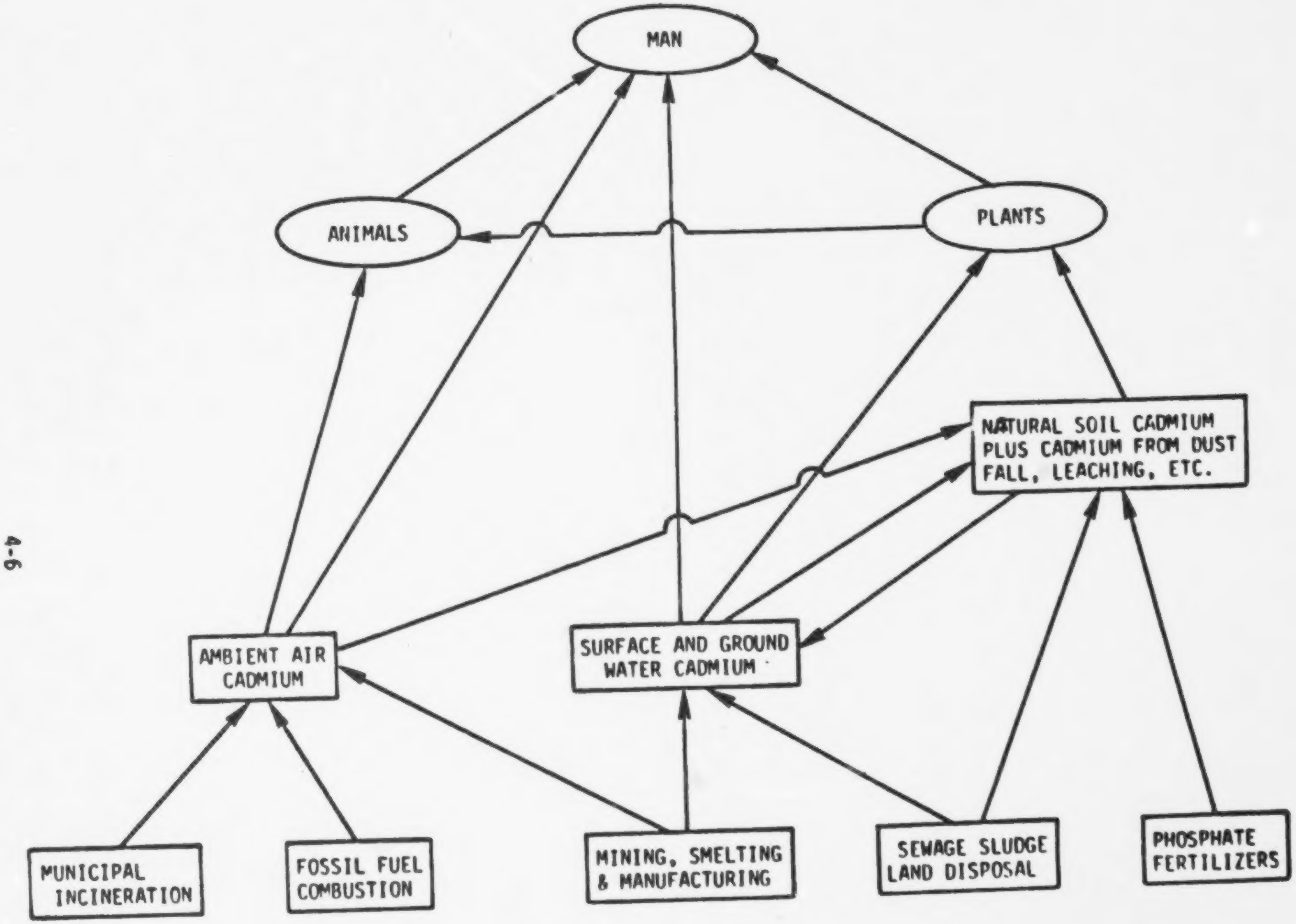

MAN
ANIMALS
PLANTS
NATURAL SOIL CADMIUM PLUS CADMIUM FROM DUST FALL, LEACHING, ETC.
AMBIENT AIR CADMIUM
SURFACE AND GROUND WATER CADMIUM
MUNICIPAL INCINERATION
FOSSIL FUEL COMBUSTION
MINING, SMELTING & MANUFACTURING
SEWAGE SLUDGE LAND DISPOSAL
PHOSPHATE FERTILIZERS

Figure 4-1. Diagrammatic representation of multi-media routes by which cadmium exposure of man can occur after dissipation of the element into the environment by anthropogenic activities.

for atmospheric cadmium appear to be definitely below 0.1 ng/m^3 and may even be close to zero in the absence of contributions from man's activities.

In contrast to the above low, frequently non-detectable background levels of cadmium generally present in air over rural or small urban areas of the United States, considerably higher concentrations have been observed in ambient air over larger urban centers or industrialized rural areas. Of historical interest, among the highest ambient air levels recorded within the United States are readings of 0.12 μg/m^3 (120 ng/m^3) obtained in El Paso, Texas in 1964 and 0.300 to 0.489 μg/m^3 (300 to 489 ng/m^3) in Shoshone County, Idaho, in 1974. Other readings taken in the United States in a 1969 survey ranged from 0.006 μg/m^3 (6 ng/m^3) in San Francisco, California, to 0.036 μg/m^3 (36 ng/m^3) in St. Louis, Mo.; and a survey in 1970 produced comparable results (Friberg et al., 1974). Since 1970, further systematic air monitoring conducted by the EPA across the United States, yielded results as discussed below. That is, ambient air levels of cadmium monitored during 1970-1974 by the EPA National Air Surveillance Network (NASN), with inputs from state and local agencies, are presented in Table 4-1 (Akland, 1976). The table indicates that the average annual values for the U.S. cities listed fall mainly within a range of 0.001 to 0.020 μg/m^3, (1 to 20 ng/m^3) with a number of averages being below the limit of detection.

Exceptions to the above pattern are found in areas where zinc or lead mining and smelting have been conducted. In particular, values from Idaho and Montana have often been 0.100 μg Cd/m^3 (100 ng/m^3) or greater, as reported in the SAROAD file (U.S. EPA, Multimedia Levels Cadmium, 1977). Faoro and McMullen (1977), however, assembled a plot of the fiftieth percentile of annual

TABLE 4-1. ANNUAL AVERAGE URBAN ATMOSPHERIC CADMIUM CONCENTRATIONS REPORTED BY NATIONAL AIR SURVEILLANCE NETWORKS, 1970-1974[a]
(L.D. = Limit of Detection)

Location	Station number	Cadmium concentration, $\mu g/m^3$				
		1970	1971	1972	1973	1974
Arizona						
Douglas	01	---	---	0.0132	---	---
Tucson	01	0.0065	0.0251	0.0045[b]	0.0045[b]	0.0062[b]
Colorado						
Denver	01	0.0102	0.0101	---	---	---
Connecticut						
Bridgport	01	0.0117	---	0.0057	---	---
Waterbury	01	. 251	0.0048	0.0174	0.0027[b]	0.0139
Georgia						
Atlanta	01	---	0.0210	---	---	---
Illinois						
Chicago	01	L.D.	0.0065	0.0030[b]	---	---
East St. Louis	01	---	0.0045[b]	0.0052	---	---
Peoria	01	0.0067	---	---	---	---
Indiana						
East Chicago	01	0.0187	0.008[b]	---	---	0.0056
Indianapolis		0.0066	0.0063	0.009[b]	---	---
Kentucky						
Ashland	02	0.0108	---	0.0093	---	0.006[b]
Covington	01	0.0048[b]	0.0049	0.003[b]	---	L.D.
Louisiana						
New Orleans	02	L.D.	0.0184	L.D.	---	---
Shreveport	01	L.D.	0.0132	L.D.	---	L.D.
Maine						
Portland	02	L.D.	0.0086	---	---	---
Michigan						
Detroit	01	0.0047	L.D.	---	---	---
Grand Rapids	01	---	0.0116	L.D.	---	---
Minnesota						
St. Paul	01	0.0060	---	0.0086	---	---
Missouri						
St. Louis	01	---	0.0155	---	---	---
Montana						
Helena	01	---	0.150	---	---	---

TABLE 4-1 (Cont.). ANNUAL AVERAGE URBAN ATMOSPHERIC CADMIUM CONCENTRATIONS REPORTED BY NATIONAL AIR SURVEILLANCE NETWORKS, 1970-1974[a]

(L.D. = Limit of Detection)

Location	Station number	Cadmium concentration, μg/m3				
		1970	1971	1972	1973	1974
New Jersey						
Camden	01	0.0063	---	---	---	---
Elizabeth	02	---	0.0167	---	---	---
Jersey City	01	0.0081	0.0056	0.0124	---	---
Newark	01	0.0125	---	0.0159	---	0.0052
Perth Amboy	01	0.0055[b]	0.0128	0.0189	---	---
New York						
New York City	01	0.0071	---	0.0060	---	---
North Carolina						
Winston Salem	02	---	0.0076	---	---	---
Ohio						
Cincinnati	01	0.0086	---	---	---	---
Cleveland	01	0.0088	---	---	---	---
Youngstown	01	0.0056	---	---	---	---
Pennsylvania						
Allentown	01	0.0081	0.0042[b]	0.0178	0.0042[b]	0.0134
Bethlehem	02	0.0140	0.0191	0.0068[b]	0.0068	---
Hazleton	01	---	---	---	0.0065	---
Philadelphia	04	---	---	0.0057	---	0.0038[b]
Scranton	01	L.D.	0.0067	L.D.	---	L.D.
Texas						
El Paso	02	0.0618	---	0.0442	0.0206	0.0242
Virginia						
Lynchburg	01	0.0135	0.0040[b]	L.D.	---	---
Wisconsin						
Kenosha	01	---	L.D.	0.0143	---	---
Racine	01	L.D.	---	0.0071	---	---

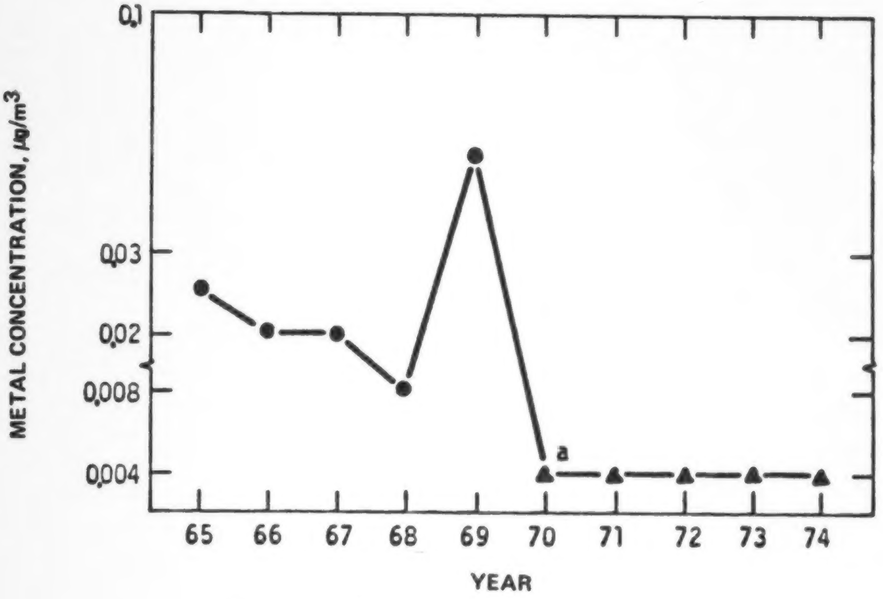
[a] Source: Akland, 1976.

[b] L.D./2 used for computation of annual average.

averages for cadmium associated with metal-industry sources at urban sites during the period of 1965-1974, in order to examine trends in levels of airborne cadmium in the United States (Figure 4-2); and it may be seen that there has been a definite large decrease in airborne cadmium emissions from industrial sources since 1970, with that trend toward lower emission levels expected to hold for the near future.

Municipal incineration of waste materials is yet another major source of cadmium emissions into the ambient air and may actually represent the single largest source of airborne cadmium exposure in terms of numbers of people directly affected and amount per year released into the atmosphere (i.e., about 131 tons annually). That is, it has been estimated that approximately 50,000,000 people are exposed to cadmium emitted by municipal incinerators, with the average exposure level being approximately 7 ng/m^3 (U.S. EPA, Assessment of Human Exposures to Cadmium, 1979). This includes cadmium emissions due both to general incineration of wastes and, more specifically, sewage sludge incineration. It has been estimated, however, that future trends for cadmium emissions associated with both types of municipal incineration will not be toward increased emissions overall, because use of emission controls on the incinerators is expected to offset possible cadmium emission increases that would otherwise accompany increased incineration loads (U.S. EPA, Sources of Atmospheric Cadmium, 1978).

A third major source of cadmium input into the atmosphere is the combustion of fossil fuels. Coal-fired and oil-fired power plants, fuel oil, diesel oil, and gasoline have all been found to be responsible for some emission of airborne cadmium. While it is difficult to establish



[a]▲ Indicates value below lower discrimination limit.

Figure 4-2. Trends in 50th percentile of annual averages for cadmium associated with metal industry sources at urban sites.

Source: Faoro and McMullen (1977).

specific current atmospheric cadmium levels explicitly associated with fossil fuel usage, it has been estimated that approximately 59 tons of cadmium are presently emitted yearly due to fossil fuel combustion, with approximately 7 tons of that being derived from coal-burning power plants. A matter of much growing concern is potential increased release of cadmium into the environment as a result of expected future increases in combustion of coal in power plants. Such increased utilization of coal is a key component in the United States effort to increase domestic energy independence. Workers at the Lawrence Livermore Laboratory have estimated that an additional one billion tons of coal may be consumed annually by 1990 (Berry and Wallace, 1974). This should be compared to the present consumption rate of 500 million tons annually (Bond et al., 1972). The expected corresponding emission of cadmium via this fuel utilization, according to EPA data (U.S. EPA, Sources of Atmospheric Cadmium, 1978), would be 16 tons annually by 1985 if emissions were controlled only at current levels. Much of this projected increase in cadmium emissions associated with expanded coal usage, however, is expected to be offset by expanded use of emission controls (U.S. EPA, Sources of Atmospheric Cadmium, 1978).

The foregoing estimates projecting that increased cadmium emissions arising both from municipal incinerators and coal-fired power plants will be largely offset by widespread use of emission control technology should be viewed with caution. According to Natusch *et al*. (1974) who studied emissions from eight coal-fired power plants: "Existing particle collection devices, although highly efficient for the removal of large particles and thus for the reduction of bulk emissions, preferentially allow the emission of the smallest, most toxic particles." Furthermore, "estimates of toxic element emissions, based on analyses of undifferentiated fly ash collected on particle precipitators, grossly underestimate the actual emissions." This is of special concern in regard to cadmium because cadmium is found to be most concentrated among the smallest respirable particles emitted from coal fires and found in fly ash (Natusch et al., 1974). These small particles are those that can most easily pass through conventional control equipment and have the highest deposition in the respiratory tract. These particles, 1-2 μm in diameter, have 3 to 18 times more of the toxic metals than fly ash particles >40 μm in diameter. Cadmium has been found to be enriched in the soil around a coal-fire power plant and also enriched in plant materials growing in this soil. The soil cadmium content correlates with the wind pattern of the area as well as the metal content of the coal burnt in the plant (Klein and Russell, 1973). Thus, not only would increased cadmium emissions from expanded coal-burning in power plants have an impact on ambient air levels, but such emissions would also impact secondarily on ground water and soil levels of cadmium via dust fall from the air.

Putting the United States' air cadmium levels into a broader perspective, it has been reported (Friberg et al., 1974) that worldwide ambient air cadmium levels are generally less than 0.003 $\mu g/m^3$ (3 ng/m^3) in rural areas, but the yearly average may range as high as 0.050 $\mu g/m^3$ (50 ng/m^3) in industrialized urban areas. In contrast, at the extreme, weekly or monthly averages around 0.50 $\mu g/m^3$ (500 ng/m^3) have been recorded in the vicinity of cadmium-emitting industries (Friberg et al., 1974).

4.2.2 Drinking Water

The cadmium found in uncontaminated rural streams is derived from natural sources and generally contains less than 1 ppb or 1 μg/l of cadmium

(Friberg et al., 1971). In some cases, however, that naturally-derived cadmium is augmented by cadmium from industrial and commercial sources. Such contamination can occur, for example, as a result of: (1) mining and smelting operations; (2) other manufacturing processes utilizing mainly cadmium (as in electroplating operations) or closely associated metals such as zinc (as in the galvinizing of steel); or (3) industrial waste disposal (as in the disposal of spent solutions from plating processes). Cadmium contamination of water also occurs secondarily to the use of phosphate fertilizers and landspreading of sewage sludge on agricultural land or the leaching of cadmium from land fill or other disposal sites. It is often difficult to state with much precision the extent to which any of the above sources of cadmium may individually contribute to water cadmium levels in any given geographic region. Nevertheless, industrial and commercial processes are usually concentrated most heavily in urban areas; it is therefore not surprising that urban waterways tend to have considerably higher water concentrations of cadmium than do rural streams. Thus, while non-polluted rural and city water often contains less than 1 μg/l, cadmium levels have been found to increase to levels as high as 10 μg/l as a result of industrial discharge or use of metal or plastic pipes (Friberg et al., 1974).

Potable water supplies in the United States have been monitored for cadmium levels since 1969, when the Community Water Supply Survey was carried out on 969 water systems by the U.S. Public Health Service (USPHS, 1970). At that time only four out of 2595 distribution samples (Taylor, 1971) exceeded the USPHS drinking-water standard of 10 parts per billion (ppb) or 10 μg/l. The average drinking-water value was 3 ppb with a maximum level of 0.11 parts per million (ppm). More recent data, through March, 1975, has been obtained by EPA (U.S. EPA, 1975); and none of the 594 analyses were above the 10 ppb standard. Particular attention in the recent survey was paid to water systems in which there is soft to "acid" water (pH 5 to 6) since cadmium and other metal dissolution from plumbing is more probable with this type of water. Two studies, done in Boston and Seattle by Deane et al. (1976) found no samples in the former locale exceeding the USPHS standard, while in Seattle 7.0 percent of the homes exceeded this value (10 ppb). Thus, in general, cadmium in drinking water does not now appear to contribute significantly to cadmium exposure for most Americans. There appears to exist, however, a need for more systematic studies to assess the extent of "pick up" of cadmium in water lines, determined by simultaneous studies of water supplies and tap water levels.

4.2.3 Soils

Soil levels of cadmium are important to man in terms of the terrestial food chain, starting with plants. Soil levels in turn reflect both geochemical and anthropogenic components. In regard to geochemical components, as suggested in Table 4-2, natural soil cadmium levels in remote areas are generally less than 0.1 ppm. Some regions, such as east-central Nevada and the Salinas Valley of California, however, have higher natural levels of soil cadmium due to higher natural content of native rocks, i.e., basaltic versus granite rocks (Fleischer et al., 1974). On the other hand, soil cadmium levels are often also greatly increased by industrial activities, as is also shown in Table 4-2.

Gowen et al. (1976) compiled urban and suburban cadmium-soil values for American cities and these tabulations appear in Table 4-3. It may be

TABLE 4-2. CADMIUM IN SOILS

Locality and type of soil	Number of samples	Depth (cm)	Cadmium content (ppm)	
			Range	Average
		Normal Soils		
U.S.S.R, tundra, podsols forest, red earth	40	A, B, and C horizons	0.01-0.07	0.06
Poland, distant from industrial areas	33	0-20	0.04 (max)	0.016
Wales, Ystwyth Valley				1.0
Maryland, Missouri, Ohio 32 m from highways[a]	4	10-15	0.12-0.52	0.26
Helena Valley, Montana, 18-60 km from smelter	17	6-10	<0.5-2[b]	1.4[b]
Annaka City, Japan, 900 m from refinery	2	40-60	0.3-0.4	0.35
Southwest Wales	4		0.3-0.5	0.4
Lower Fraser Valley, British Columbia	33	Surface		0.88
		Contaminated Soils		
Poland, industrial areas	67	0-20	0.3-0.8 (max)	0.17-0.28
Wales, Ystwyth Valley, contaminated			1.5-3.0	
Maryland, Missouri, Ohio, 8 m from highways[a]	4	0.5	0.90-1.82	1.28
Helena Valley, Montana, 1 km from smelter	7	0.10	26-160	72
Annaka City, Japan				
150-250 m from smelter		Surface	23-88	
900 m from smelter		5	44	
Poland, 600 m from zinc metallurgical factory	1 1	0-10 15-30	250 110	
Southwest Wales, Swansea, 1.5 km from contaminated area			26	
Bartlesville, Oklahoma, 1500 ft from smelter		12.5-27.5	450	
British Columbia, 15 m from smelter	4	Surface	7.9-95.2	49.0
Grand Rapids area, Michigan				
Residential area	70	0-5		0.41
Agricultural area	91	0-5		0.57
Industrial area	86	0-5		0.66
Airport	7	0-5		0.77

[a] Samples collected near U.S. 1, Beltsville, MD; Washington-Baltimore Parkway, Bladensburg, MD; Interstate 29, Platte City, MO; Seymour Road, Cincinnati, OH.

[b] These values probably reflect some contamination.

Source: Adapted from Fleischer et al., 1974.

TABLE 4-3. CONCENTRATIONS OF CADMIUM IN URBAN AND SUBURBAN SOILS--1972[a]

SMSA	Number of samples		Cadmium, ppm[b]			Percent of positive detections
			Arithmetic mean	Geometric mean	Range	
Des Moines, IA	59	Urban	0.89	0.640	0.1 - 3.56	100
	25	Suburban	0.28	0.124	0.00 - 1.76	80
Fitchburg, MA	26	Urban	0.13	0.059	0.00 - 0.70	62
	10	Suburban	0.13	0.051	0.00 - 0.38	60
Lake Charles, LA	16	Urban	0.36	0.015	0.00 - 5.32	25
	54	Suburban	0.01	0.002	0.00 - 0.11	7
Pittsburgh, PA	51	Urban	1.21	0.743	0.00 - 4.95	98
	138	Suburban	0.90	0.454	0.00 - 8.03	93
Reading, PA	10	Urban	0.63	0.261	0.00 - 1.70	90
	41	Suburban	0.25	0.039	0.00 - 2.45	44

[a] Source: Gowen, et al, 1976.

[b] Sensitivity to 0.5 ppm.

seen that urban areas almost invariably have higher cadmium amounts than suburban areas. Also, industrialized areas typically have higher levels than less industrialized regions; Fitchburg, MA, for example, had suburban and urban values of 0.13 ppm each in comparison to readings of 0.25 and 0.65 ppm for Reading, PA, and values of 0.91 and 1.21 ppm for Pittsburgh, PA. Consistent with this, in another study, Yost et al. (1975) found higher-than-normal (>0.4 ppm) levels of 2.5 or 14.0 ppm in samples obtained in East Chicago, Indiana.

Significant contamination of soil with cadmium also occurs in certain rural areas as a result of man's activities. For example, the study of Munshower (1972) found soil levels varying as a function of distance from a smelter in East Helena, Montana. The levels ranged from 27.3 ppm (0 to 5.0 cm in depth) at 2.4 km away to 1.5 ppm at 33.8 km away, illustrating well that cadmium particles in the air can settle to the ground and add measurably to soil cadmium levels.

Also, agricultural use of land adds to the soil-cadmium burden. In that regard, a significant contribution comes from phosphate fertilizers, with cadmium values varying from 0.15 ppm in untreated soils to 3.38 ppm in lands dressed with phosphate fertilizers. Another practice that could contribute significantly to soil cadmium levels in agricultural land, however, is the increasing use of landspreading of municipal sewage sludge and other cadmium-containing materials on commercial crop lands; and this is a matter of considerable concern for several regulatory agencies such as the EPA and FDA.

The reason for concern about increased spreading of sewage sludge on agricultural land is the fact that the cadmium content of such sludge has been found to range from a few ppm to several thousand ppm; indiscriminate increased usage of sludge for fertilization of croplands could therefore result in a major new source of contamination of foodstuffs and significant increases in dietary cadmium exposure of the general population. The magnitude of the current and potential future sludge problem is illustrated by the data contained in Appendix A.

Appendix A reports amounts of sewage sludge containing varying concentrations of cadmium disposed of by certain United States cities, including by means of landspreading on agricultural land. The information listed in Appendix A is based on data compiled by the EPA Office of Solid Waste Management in 1976 and reported in two separate sources, i.e., EPA Multimedia Levels Cadmium (1977) and Impact of Annual Cadmium Application Rates on Current Municipal Sludge Landspreading Practices (1978). The sludge production from the cities listed in Appendix A totals 3706 dry mt/day produced, and approximately 672 dry metric tons (mt) per day were reported as being agriculturally landspread, which represents about 25 percent of the sludge generated. It is important to note, while many municipalities produce sludge with relatively low cadmium content (less than 10-15 ppm), many other towns and cities produce sludges containing cadmium levels in excess of 100 ppm (100 mg/kg). Low cadmium content sludge, however, is not the only kind that has been spread on agricultural land. Some sludges having cadmium contents in excess of 100 ppm have been used. For example, one town was reported as having landspread its daily production of 2 dry mt/day of sludge, with a cadmium content of 3171 ppm, on agricultural land. Also, from among the 41 "unknown" cities which produce sludges with cadmium concentrations of 1-970 ppm, ten cities were reported as producing 70 dry mt/day of sludge with cadmium content above 25 ppm that was agriculturally landspread. Other data discussed below under "Food" as a source of cadmium exposure provides a perspective on the implications of agricultural spreading of sewage sludge with varying cadmium concentrations, and phosphate fertilizers as well, for consequently increased soil and crop cadmium content.

4.2.4 Food

Cadmium contamination in air, water, and soil not only affects man directly through contact with those media, but also through the infiltration of the metal from those sources into man's food chain. No effort will be made here to trace in detail cadmium's transport via the food chain to man. It should be noted, however, that man depends on five major categories of food sources: (1) land plants, (2) land animals and animal products, (3) freshwater fish, (4) marine fish and free-moving crustaceans, and (5) shell fish.

Incorporation of cadmium into the above dietary food elements appears to occur through a variety of mechanisms, with several sometimes operating simultaneously. From among such mechanisms listed by an EPA assessment (Multimedia Levels Cadmium, 1977), the following appear to be of most importance:

(1) Uptake from soils by roots of food plants. This is a pH dependent process and may occur:

   a. Naturally where cadmium is a normal constituent of soils.
   b. As an impurity (cadmium oxide) in phosphate-treated soils, especially with "superphosphate" fertilizer use.
   c. In soils fertilized by sewage sludge containing cadmium.

d. By soil contamination from runoff of mine tailings or from electroplating washing process.

(2) Meat animals may accumulate cadmium in liver and kidney from feed crops that take up the metal from contaminated and naturally high-cadmium content soil.

(3) Mollusks and crustaceans normally concentrate cadmium from ambient waters, as do most other aquatic organisms.

Oral ingestion of food probably represents the single most important source of cadmium in man, especially in non-smokers. It may, in part, also represent a secondary exposure from airborne cadmium to the extent that airborne cadmium probably contributes some amount of the metal to food via deposition in water and on land from which food crops and animals are obtained. No thorough analysis of the contribution of airborne cadmium to food will be attempted here, but it should be kept in mind in considering the information that follows. Another issue not addressed in detail here, but important for putting the present discussion into perspective, is that of how much of the cadmium eventually showing up in food is derived from naturally occurring sources and how much accumulates secondarily from man's industrial and waste-disposal activities.

In an earlier EPA analysis (Multimedia Levels Cadmium, 1977) it was noted that foods average about 0.05 ppm cadmium (wet weight), but there is wide variation across different food items, with maximum concentrations depending on the source from which they were obtained. The amounts found in different food categories in the U.S.A. in the late 1960's were reported by the United States Food and Drug Administration (FDA) to be as indicated in Table 4-4, as estimated from several studies (Corneliussen, 1970;

TABLE 4-4. CADMIUM CONTENT IN DIFFERENT FOOD CATEGORIES IN THE U.S.A.[a,b]

	Cadmium, μg/g wet weight			
	1968-1969		1969-1970	
Type of food	No. >0.01	Maximum	No. >0.01	Maximum
Dairy products	10	0.09	9	0.01
Meat, fish, and poultry	21	0.06	22	0.03
Grain and cereal products	27	0.08	27	0.06
Leafy vegetables	27	0.08	28	0.14
Legume vegetables	16	0.03	10	0.04
Root vegetables	24	0.08	27	0.08
Garden fruits	25	0.07	27	0.07
Fruits	15	0.04	10	0.07
Oils, fats, and shortening	27	0.13	28	0.04
Sugar and adjuncts	18	0.07	9	0.04
Beverages	8	0.04	9	0.04
Potatoes	--	--	29	0.08

---

[a] Source: Corneliussen, 1970; Duggan and Corneliussen, 1972.

[b] Cadmium was analyzed by atomic absorption and/or polarography at a sensitivity of 9.01 μg/g.

Duggan and Corneliusson, 1972). Concentrations of cadmium found more recently by FDA in adult foods are seen in Table 4-5 (U.S. Dept. of Health, Education and Welfare, 1975). Adult foods consistently found in the surveys to have high levels of cadmium are: beef liver, hamburger, leafy vegetables, root vegetables, potatoes, grains and cereal products, and refined sugar products. Relatively high standard deviations for virtually all foods listed in Table 4-5, however, also suggest that quite high concentrations can be found in some samples of nearly every food type.

Estimates by the FDA of the contribution of different foodstuffs to daily adult dietary intake are shown in Tables 4-6 and 4-7, and the percentages of total daily cadmium intake estimated to be obtained via ingestion of different food groups are illustrated in Figure 4-3. As seen there, most of the food groups listed above as high in cadmium constitute major portions of the typical adult diet and contribute the largest percentages of daily dietary cadmium intake.

A matter of considerable interest is the estimation of daily dietary intake for Americans. Noteworthy in that regard are results from Total Diet Studies (market basket) surveys conducted by the FDA over a seven year period (1968-1974). As shown in Tables 4-6 and 4-7, cadmium intake from all food groups varied somewhat from year to year (totaling 36 and 51 μg/day for the two years shown in the tables for the "typical" teenage American male). The average of the median levels obtained over the seven year survey period was 33 μg/day, while the seven-year average of the means was 72 μg (U.S. Dept. of Health, Education and Welfare, 1975). This suggests that most individuals have intake levels below 30 to 50 μg/day, but some may have intakes substantially above 70 μg/day.

TABLE 4-5. CADMIUM CONTENT OF SELECTED ADULT FOODS[a]

Commodity	No. of samples	Average, ppm	Standard Deviation, ppm
Carrots, roots fresh	69	0.051	0.077
Lettuce, raw crisp head	69	0.062	0.124
Potatoes, raw white	71	0.057	0.139
Butter	71	0.032	0.071
Margarine	71	0.027	0.048
Eggs, whole fresh	71	0.067	0.072
Chicken fryer, raw whole or whole cut up	71	0.039	0.088
Bacon, cured raw, sliced	71	0.040	0.160
Frankfurters	69	0.042	0.111
Liver, raw beef	71	0.183	0.228
Hamburger, raw ground beef	71	0.075	0.122
Roast, chuck beef	71	0.035	0.034
Wheat flour, white	71	0.064	0.150
Sugar refined, beet or cane	71	0.100	0.709
Bread, white	70	0.036	0.063
Orange juice, canned frozen concentrate	71	0.029	0.095
Green beans, canned	71	0.018	0.072
Beans, canned with pork and tomato sauce	71	0.009	0.000
Peas, canned	71	0.042	0.113
Tomatoes, canned	71	0.042	0.113
Diluted fruit drinks, canned	71	0.017	0.052
Peaches, canned	71	0.036	0.061
Pineapple, canned	71	0.059	0.153
Applesauce, canned	71	0.020	0.027

[a] Source: U.S. Department of Health, Education, and Welfare, 1975.

TABLE 4-6. FOOD GROUPS BY MEAN CADMIUM CONTENT AND THEIR CONTRIBUTION TO DAILY CADMIUM INTAKE[a]

Food group	Concentration, ppm Mean	Cadmium intake μg/day	Percent of total daily diet	Contribution to daily cadmium intake, %
Leafy vegetables	0.051	3.18	2.0	6.2
Potatoes	0.046	9.11	7.0	17.8
Fruits	0.042	9.38	7.4	18.3
Grains and cereals	0.028	11.66	12.6	22.8
Oils, fats, and shortening	0.027	1.36	1.8	2.7
Root vegetables	0.021	0.76	1.2	1.5
Garden fruits	0.019	1.71	3.0	3.4
Meats, fish, and poultry	0.0093	2.49	9.9	4.9
Sugars and adjuncts	0.0083	0.68	2.8	1.3
Legume vegetables	0.006	0.42	2.5	0.8
Beverages	0.0057	6.49	23.9[b]	12.7
Dairy	0.005	3.94	25.9	7.7

[a] Source: Mahaffey et al., 1975.

[b] Includes water.

TABLE 4-7. CADMIUM INTAKE OF TEEN-AGE MALES BY FOOD CLASS[a]

Food class	Average consumed g/d	Cadmium* residue ppb	Cadmium intake µg/d
Dairy products	704	5.7	4.0
Meat, fish, poultry	262	15.3	4.0
Grain and cereal products	424	23.3	9.9
Potatoes	177	48.0	8.5
Leafy vegetables	54	40.5	2.2
Legume vegetables	66	6.3	0.4
Root vegetables	32	32.3	1.0
Garden fruits	88	14.7	1.3
Fruits	222	3.0	0.7
Oils, fats, shortening	72	15.3	1.1
Sugars and adjuncts	83	10.0	0.8
Beverages (including water)	684	3.0	2.1
Total	2868		36

*Trace values assumed as 10 ppb.

[a] From U.S. Dept. of Health, Education and Welfare. "Compliance Program Evaluation, FY '74 Total Diet Studies (7320.08)". Food and Drug Administration, Bureau of Foods, 1975.

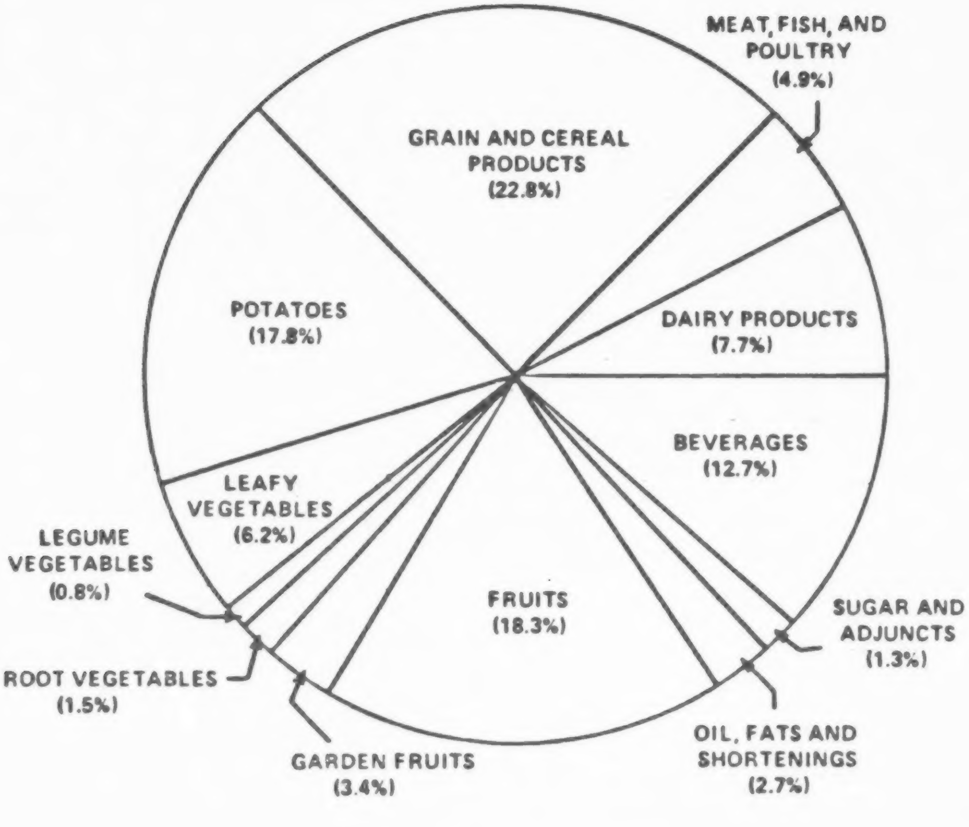


Figure 4-3. Contribution of food groups to cadmium intake.

Source: Shibko and Braude (1978).

Also of interest in regard to the issue of daily cadmium intake in the diet of the U.S. population are the results of a collaborative study, which was carried out jointly in the United States, Sweden and Japan (Kjellström, 1979) and included measurement of daily fecal cadmium excretion for human volunteers in each country. Based on observed fecal cadmium values, which may better reflect actual dietary cadmium intake than the above "market basket" surveys, adult dietary intake of cadmium in a Dallas, Texas, population was reported to average approximately 18 μg/day for non-smokers. This arithmetic mean intake was associated with a standard deviation of ± 8 μg, indicating that diets vary considerably among members of that population in terms of cadmium content. This is in keeping with other observations obtained by other EPA-sponsored fecal excretion studies on Chicago populations in 1974 and 1975, as summarized in Table 4-8, along with the 1975 Dallas survey data. In fact, based on the observed distributions, the intake of five percent of the individuals studied exceeds 33 μg/day and for one percent, approximately 50 μg/day. It thusly appears that an average daily dietary cadmium intake for Americans can reasonably be estimated to be within the range of 10 to 50 μg/day; however, it is also clear that significant numbers (≅ 1 percent) of adults likely exceed 50 μg/day of dietary cadmium intake.

While the above estimates are among the best available for current levels of daily dietary cadmium intake, they may not necessarily be accurate indicators of future American dietary exposure to cadmium. Rather, increased amounts of dietary cadmium could be ingested in the future if use of high cadmium-containing phosphate fertilizers on U.S. crop lands is expanded or if uncontrolled landspreading of cadmium-contaminated sewage sludge on agricultural land were permitted.

TABLE 4-8. DISTRIBUTION OF DAILY DIETARY CADMIUM INTAKE (μg/day) OF U.S. POPULATIONS AS DETERMINED BY FECAL EXCRETION STUDIES

Study Population	Year	N	Percent of Population Which Exceed Displayed μg/day Value 50%	10%	5%	1%
Chicago	1974	192	13.7	28.5	35.1	51.8
Chicago	1976	199	9.1	28.8	40.2	74.3
Dallas	1975	86	12.5	20.8	25.6	34.4
		$\bar{x}$ (μg/day) =	11.8	26.0	33.6	53.5

Several studies provide important information on the likely impact of cadmium loading of agricultural land on soil and crop cadmium contents. For example, at a 1 kg/ha cadmium application rate, Dowdy and Larson (1975) found that lettuce cadmium increased five-fold compared to control levels, while carrots, radishes, and potatoes showed a two-fold cadmium increase and sweet corn leaves and grain increased from 0.26 to 1.32 ppm cadmium and from 0.02 to 0.05 ppm cadmium, respectively. In a similar study, Clapp _et al_. (1976) showed that, at a 5.1 kg/ha cadmium loading rate on sandy soil in Minnesota, the cadmium content of field corn leaves normally fed to livestock increased five-fold, but the corn grain levels were not changed.

Maclean (1976) applied 0, 2.5, and 5.0 ppm cadmium (approximately 0, 5.5, and 11 kg Cd/ha) to Grenville loam soil with a neutral pH of 7.1 and observed the effect on cadmium uptake by several vegetables and field crops. The results obtained are shown in Table 4-9 and indicate that many vegetables and root crops increased their cadmium uptake by five-fold at the 5.5 kg/ha cadmium application rate. At the same application rate, oats and soybeans, as intermediate cadmium accumulators, increased their cadmium content by six-fold, while tobacco and lettuce, as high cadmium accumulators like Swiss chard, had more than 10-fold increases in cadmium. It should be noted that the increases observed with cadmium additions to the soil were superimposed on already high levels seen in the control plants.

When soil pH is taken into account, then even more striking effects of cadmium loading on crop uptake of the metal are seen. Specifically, the uptake of cadmium by many plants is dramatically increased by acidic soils, as illustrated in Figure 4-4 for Swiss chard. The practical consequences of this for impications of sewage-sludge landspreading on agricultural land

TABLE 4-9. CADMIUM CONTENT OF SEVERAL CROPS AND TISSUES AS A FUNCTION OF CADMIUM LOADING OF SOIL[a]

		Cd Content of Crop Tissue, ppm		
		Added Soil Cd, ppm		
Crop	Tissue	0	2.5	5.0
Timothy	Tops	0.21	1.04	1.41
Alfalfa	Tops	0.28	1.34	1.72
Corn	Tops	0.22	1.84	2.68
Oat	Straw	0.29	2.30	3.70
Oat	Grain	0.21	1.50	2.07
Soybean	Veg.	0.71	3.95	4.88
Soybean	Grain	0.29	1.88	2.51
Tomato	Veg.	0.51	5.26	6.46
Tomato	Fruit	0.23	0.99	1.03
Potato	Tops	0.58	3.46	7.35
Potato	Tubers	0.18	0.89	1.09
Carrot	Tops	0.46	5.66	7.70
Carrot	Roots	0.24	2.53	2.65
Lettuce	Tops	0.66	7.72	10.36
Tobacco	Tops	0.49	5.41	11.57

[a] (From Maclean, 1976) Grenville loam pH = 7.1.

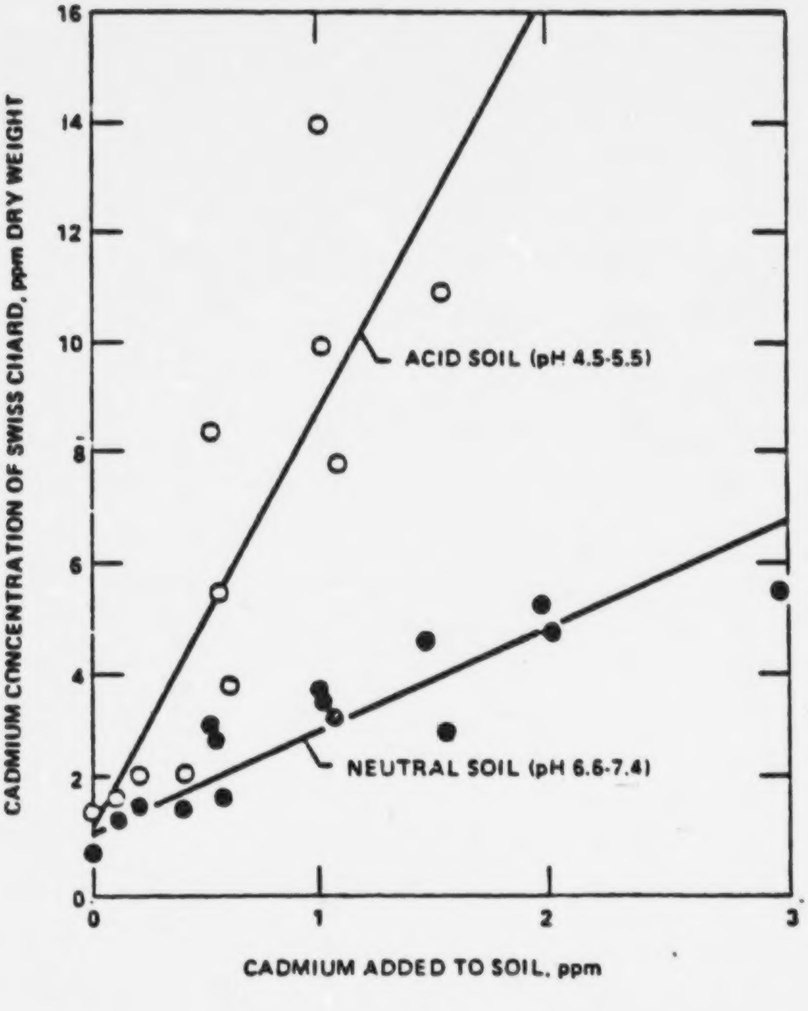


Figure 4-4. Effects of soil pH on cadmium uptake by vegetables.

Source: Lucas et al. (1978).

are well demonstrated by the data in Table 4-10 showing the results of studies on field sites that received sewage-sludge treatment for several years. The actual annual loadings on a kg Cd/ha basis are not known, but the sludge cadmium content from cities 1, 4, 9, and 13 were 100, 22, 169, and 683 ppm, respectively. Sites for cities 1 and 4 had not received sludge since 1975 and for 9 and 13 not since 1973 and 1974, respectively, with the data in Table 4-10 being for crops grown in 1976. Not only do the results illustrate the importance of soil pH in determining crop uptake of cadmium, but they also show that cadmium persists in the soil in a form available for crop uptake even after cessation of sludge spreading. Thus, where uncontrolled spreading of high cadmium-containing wastes (such as sewage sludge) on agricultural land occurs, increased dietary ingestion of cadmium could result from increased cadmium uptake by food crops grown on those soils in years to come.

Phosphate fertilizers also contain appreciable levels of cadmium as a contaminant, and their widespread use on agricultural land can constitute a significant source of cadmium available for uptake by a variety of plants beyond the naturally occurring trace amounts of the element present in most soils. Levels of cadmium in phosphate fertilizers used in the United States domestic consumption can vary considerably from 9 mg/kg (9 ppm) for Florida phosphate ore to Western ore levels of 130 mg/kg (130 ppm) (EPA, 1974).

Schroeder and Balassa (1963) first suggested that cadmium contamination of soils from this source might lead to increased uptake of cadmium into the food chain. A number of other studies have appeared subsequently and have shown that cadmium uptake from fertilizer into plants is related to a

TABLE 4-10. Cd CONTENT OF SOILS AND CROPS GROWN ON ACID AND LIMED SLUDGED SITES[a]

City	Sludged	Limed	Soil			Lettuce leaf	Swiss Chard		Soybean		Oat			Orchardgrass	
			pH	Total	DTPA	ppm	D.	W.D.	Leaf	Grain	Boot	Fodder	Grain	1st	2nd
							ppm		ppm			ppm		ppm	
1	1967-75	No	5.08	3.30	2.07	17.53	28.03	23.18	2.05	0.48	----	----	----	----	----
	1967-75	Yes	6.15	3.42	1.98	7.52	14.03	10.43	1.02	0.37	----	----	----	----	----
	No	No	5.75	0.15	0.06	1.07	0.58	0.64	0.24	0.20	----	----	----	----	----
	No	Yes	6.54	0.14	0.06	0.45	0.34	----	0.18	0.13	----	----	----	----	----
4	1962-75	No	5.36	1.06	0.64	4.00	2.29	**	0.89	**	0.37	0.59	0.23	0.41	0.56
	1962-75	Yes	6.22	0.97	0.52	1.36	0.89	**	0.43	**	0.18	0.19	0.07	0.21	0.26
	No	No	5.91	0.20	0.10	0.84	0.45	**	0.11	**	0.11	0.12	0.05	0.30	0.57
	No	Yes	6.64	0.20	0.07	0.71	0.15	**	0.10	**	0.11	0.09	0.04	0.17	0.17
9	1961-73	No	4.92	2.75	1.29	20.41	37.09	**	4.93	1.07	2.42	5.03	2.12	1.63	1.67
	1961-73	Yes	6.26	2.88	1.22	4.64	2.90	**	0.68	0.38	0.40	0.79	0.38	0.56	0.66
	No	No	4.93	0.30	0.15	1.61	**	**	0.44	0.20	0.25	0.50	0.22	0.56	0.34
	No	Yes	6.31	0.18	0.09	0.63	0.78	**	0.17	0.08	0.11	0.12	0.04	0.24	0.17
13	1967-74	No	5.70	9.58	6.30	49.86	46.16	22.96	5.93	1.50	6.55	10.94	3.38	2.31	3.69
	1967-74	Yes	6.37	6.79	3.70	9.91	11.02	5.94	0.90	0.68	0.61	0.86	0.54	0.70	1.17
	No	No	5.22	0.14	0.09	1.47	1.30	0.96	0.34	**	0.11	0.10	0.11	0.12	0.17
	No	Yes	6.21	0.13	0.07	0.58	0.41	0.45	0.25	0.11	0.10	0.06	0.07	0.06	0.16

[a] Source:
** = No sample due to animal damage
---- = Crop not grown

number of factors such as the amount of phosphate applied, soil type, soil pH, types of plants grown, and parts of plants intended for foodchain use (Williams and David, 1973, 1976; Lee and Keeney, 1975; Miller et al., 1976; Andersson, 1976; Reuss et al., 1976).

As expected, soil pH is important in the relative uptake of cadmium from phosphate treated soils into plants, with increasing pH leading to reduced cadmium uptake. Soil type as measured by cation exchange capacity (CEC) appears to be another important factor in transfer of cadmium from phosphate fertilizer into vegetation grown on it (Miller et al., 1976). The relative uptake of cadmium by plants also varies considerably with the type of plant grown on phosphate-dressed soils, leafy vegetables and grains showing relatively greater uptake than forage crops (Williams and David, 1973 and 1976; Reuss et al., 1978). Andersson (1976), in his studies of plant-available cadmium in soils, however, has found that soil levels of cadmium are not likely to be affected if the cadmium content of phosphate fertilizers is maintained below 8 ppm (mg/kg).

Since phosphate fertilizers and sewage sludge both add to the cadmium burdens of agricultural land, it would be of interest to consider the relative quantitative impact of the future intended use of sewage sludge with current use of phosphate fertilizers.

In Sweden, where sewage sludge use is limited and is regulated at a maximum permissable level of 15 ppm, the total amount of cadmium in sludge for 1973 was calculated to be 1260 kg cadmium (Stenstrom and Vahter, 1974), as compared to a corresponding cadmium total of ca. 10,000 kg cadmium in phosphate fertilizers.

In the United States, it is much more difficult to compare the relative impact of these two sources with respect to increasing the soil burden of agricultural lands. For one thing, it is to be expected that sewage sludge use will increase in the future. While the relative growth in phosphate fertilizer use will probably be less, phosphate fertilizer consumption is widespread and without the extensive use of controls that will presumably apply to sewage sludge use (Solid Waste Disposal Facilities: Proposed Classification Criteria - EPA, 1978).

In this regard, Lee and Keeney (1975) have calculated that in Wisconsin cadmium added to agricultural land amounts annually to about 2150 kg/year. They also estimate that the potential contribution of cadmium from waste-water sludges would be ca. 1700 kg/year if all the sludge produced in Wisconsin were spread on the land. This total volume was estimated to contain a median cadmium concentration of 18 ppm (dry weight) in waste originating from 35 municipalities that serve 75 percent of the sewered population. On a total basis, it would appear that phosphate fertilizers are a more significant source of cadmium than sewage sludge in one particular state in the U.S. However, these authors argue that on a concentration basis, sludge may have the potential for increasing soil concentrations (mg Cd/kg soil) more significantly because of the much higher rates of application used. They calculate that, in Wisconsin, 186 years of phosphate fertilizer application would be required to equal a single 9 metric ton/hectare sewage sludge addition (at an 18 ppm median cadmium concentration level in the sludge).

There are certain factors which must be kept in mind regarding phosphate fertilizer as a source of cadmium: (1) the cadmium content of the phosphate as a function of the source of the phosphate and (2) the relative absence of any controls on the use of phosphate when compared to the developing picture of regulation for landspreading of sewage sludge. Thus, any change in the sources of phosphate fertilizers with respect to domestic consumption may alter the total amounts of cadmium introduced onto agricultural land. Furthermore, the relative lack of any controls on the use of phosphate fertilizer with respect to increasing the cadmium levels of crops and other components of the foodchain, i.e., soil pH, types of soil, and types of plants, suggest that cadmium concentration in the food chain from this source is likely to continue.

It should be noted that much of the emphasis here on the effects of addition of materials to agricultural soils that raise soil cadmium levels is based on an awareness of the extreme difficulty in removing this added cadmium burden once in place. For example, the Japanese have had little success in restoring cadmium-contaminated crop land to its former productive use despite very extreme attempts at chemical debreedment of the cadmium in the soil (Friberg et al., 1974).

4.2.5 Other Sources

Cigarette smoking represents another major source of cadmium intake for many Americans. In fact, cadmium from cigarettes represents a substantial additional burden for smokers beyond that derived from food and other sources, putting smokers at special risk as discussed later. Amounts of respiratory intake from cigarettes range from 4 to 6 μg from two packs smoked per day. Amounts obtained from lesser use of cigarettes are shown in Table 4-11 along with a summary of contributions from other media to normal retention of cadmium, as reported by EPA (Multimedia Levels Cadmium,

TABLE 4-11. MEDIA CONTRIBUTIONS TO NORMAL RETENTION OF CADMIUM[a]

Medium	Adult	Exposure level	Daily retention (μg)
Ambient air	x 20 m^3/day	0.03 μg/m^3	0.15[b]
Water	x 1 liter/day	3 μg/l	0.36[c]
Food	x 2 kg/day	50 μg/day	3.0[d]
Cigarettes			
Packs/day		μg/day[b]	
1/2		1.1	0.70[e]
1		2.2	1.41[e]
2		4.4	2.82[e]
3		6.6	4.22[e]

[a] Modified from: Deane L. G., D. A. Lynn, and N. F. Surprenant. Cadmium: Control Strategy Analysis. ECA Cong., Bedford, Mass. U.S. Environmental Protection Agency. 1976.

[b] Based on 25 percent deposition and assuming 100 percent absorption of deposited amount.

[c] Based on average American drinking water level of 3 ppb and assuming 6 percent absorption from gastrointestinal tract.

[d] Based on 6 percent absorption from gastrointestinal tract.

[e] Based on 0.11 μg Cd per cigarette and 6.4 percent retention rate demonstrated by Lewis, G. P., W. J. Jusko, L. L. Coughlin, and S. Hartz. Cadmium accumulation in man. Influence of smoking, alcoholic habit and disease. J. Chron. Dis. 25:712-726, 1972.

1977). It should be noted that cadmium levels in cigarettes would be expected to increase greatly in the event of cadmium-containing fertilizers or sewage sludge being spread on tobacco fields, in view of tobacco being one of the most avid accumulators of cadmium among crop plants. Prohibition of spreading high-cadmium content sludge on tobacco crop land, however, is expected to occur as part of future EPA regulatory actions (Solid Waste Disposal Facilities: Proposed Classification Criteria-EPA, 1978).

4.3 HEALTH EFFECTS SUMMARY

A wide variety of biological and adverse health effects of cadmium were described in earlier sections of this report, and the evidence for them from animal experiments and human epidemiologic studies was evaluated. At this point in discussing risk assessment it would be useful to summarize the more important health effects that appear to be of most concern in cadmium exposure.

Acute effects of cadmium on the lungs are of most immediate concern in cases of exposure to high levels of the metal via inhalation. Lethal levels of cadmium depend in part on particle size, form of metal compound encountered, and other factors. Estimates of LD_{50} exposure levels in rats and mice fall around 25 mg/m^3 for 30 min for particle size of 0.2 μ; and, for man, total pulmonary retention of 4 mg of cadmium after acute inhalation exposure is often fatal. Quite serious adverse effects, e.g., the induction of pneumonitis, are found at inhalation exposure levels far below lethal doses; significant lung impairment in man, for example, has been noted at cadmium-oxide fume levels below 1.0 mg/m^3.

In situations involving long-term cadmium exposure, especially at low to moderate levels, cadmium effects on the kidney appear to be the most crucial ones, with renal dysfunction currently widely accepted as the "critical effect" in terms of assessment of requisite exposure levels for induction of toxic actions of the metal. The renal dysfunction referred to involves cadmium-induced disruption of normal functioning of renal tubular cells, resulting in increased urinary excretion of proteins (proteinuria), amino acids (aminoaciduria), glucose (glucosuria) and other substances such as calcium. Proteinuria, as one of the earliest signs of the renal dysfunction typically manifested, is therefore a highly useful indicator reflecting or indexing the onset of cadmium renal toxicity. Estimations of amounts of cadmium accumulation in the kidney necessary for the induction of damaging effects resulting in proteinuria are important, therefore, in order to calculate external exposure levels from various sources necessary to induce the "critical effect" of renal dysfunction. Presumably, limiting cadmium exposures to levels assuring protection against the induction of proteinuria would, then, in essence provide protection against any other more serious adverse effects as well. This issue is discussed further in the present chapter under consideration of dose-effect dose-response relationships.

As stated in the discussion above, renal tubular dysfunction is the critical effect associated with chronic exposure to cadmium and is also that effect most relevant for populations at large. Two aspects of cadmium-induced renal dysfunction which are of paramount significance in any health risk assessment of cadmium can be framed as questions: 1) Is cadmium-induced renal dysfunction, as indexed by tubular proteinuria, reversible or irreversible in nature; and 2) regardless of its reversibility or irreversibility, is the presence of renal tubular dysfunction to be taken as a significant health effect?

In regard to the first issue, Piscator (1977) has reported data on eighteen cadmium workers that conclusively demonstrate the persistence of renal dysfunction, as indexed by tubular proteinuria, approximately twenty years after cessation of exposure. What is even more notable is the fact that irreversibility exists even at relatively low initial excretions of protein. Also, Kazantzis (1977) has reported on his study of six cadmium workers first surveyed in 1961, with five subjects surviving for the total survey period of 15 years. All of these workers were presumably exposure free or were in reduced exposure settings after the first survey. All members of this study group displayed persistent tubular proteinuria at the second time point in the survey. Thus, available data clearly indicate that, for at least some individuals, cadmium-induced renal proteinuria can be irreversible.

As to the issue of proteinuria-indexed renal tubular dysfunction being a significant health effect, the available evidence strongly indicates that it is indeed a health effect worthy of concern. Here, one can consider both the fact that tubular dysfunction, i.e., a systemic functional lesion, is itself a demonstrable impairment of the proper functioning of a vital organ, the kidney and, also, perhaps more importantly, the onset of tubular proteinuria signals the precarious status of an organ that has a substantially reduced reserve capacity for accommodating any additional stress and is functionally on the way to further, more involved dysfunction. Also, based on the fact that cadmium accumulation in the kidney occurs over many years and such accumulation does not markedly decay at the onset of tubular dysfunction, it is logical that tubular dysfunction would not be a transitory event since the lesioning agent, cadmium, remains at the target site to persist in imparting damage; nor would this early dysfunction necessarily be the sole extent of renal injury.

The data of Kazantzis (1977) supports the premise that a kidney already manifesting tubular proteinuria is at high risk for further functional complications. Of the six subjects in the survey noted earlier above, one person developed ostiomalacia and a second suffered from chronic renal stone problems. All subjects showed persisting hypercalcuria and hypophosphataemia; of five subjects studied for uric acid clearance, all of them showed abnormally high clearance. Furthermore, four subjects had aminoaciduria, and five individuals had glycosuria. Of these numbers in each category, uric acid clearance became elevated in three cases after the first survey; three cases of glycosuria, two cases of aminoaciduria, one case of hypercalcuria and one case of hypophosphataemia similarly developed subsequent to the first survey.

The reader is directed to further discussion of the above issues by clinical workers in the area of cadmium health effects, as reported in the Proceedings of the First International Conference on Cadmium, San Francisco, 1977, pp. 243-250. In addition, a recently published report (Kjellström et al., 1979) should be noted concerning the observation of statistically significant increases in renal disease mortality rates among battery plant workers chronically exposed to high levels of cadmium in the workplace.

Whereas the above conceptualization of renal damage being the "critical effect" associated with cadmium toxicity has much evidence to support it, it should be noted that certain other suggestive evidence hints at other effects possibly occurring as the result of chronic low-level cadmium exposure. These effects include, for example, the following: (1) certain "subtle" hormone effects that likely underlie reductions in plasma testosterone concentrations observed with cadmium exposures in the absence of signs of renal damage or severe testicular necrosis; (2) effects on reproduction and development, e.g., reductions in birthweights seen after oral exposure of pregnant animals and having some parallels in reports in the human epidemiology literature; (3) immunosuppression effects demonstrated to occur in animals at low oral exposure levels, but not yet confirmed in humans; and (4) certain mutagenic and carcinogenic effects observed in *in vitro* or *in vivo* animal experiments or reported in human epidemiology studies. In regard to all four of the above examples, however, insufficient evidence currently exists to warrant any of them being treated now as key health effects associated with chronic cadmium exposures at environmentally relevant levels. Rather, of crucial importance for present purposes are the much more conclusively demonstrated cadmium-induced renal effects discussed earlier above and quantitatively assessed below.

4.4 DOSE-EFFECT AND DOSE-RESPONSE RELATIONSHIPS OF CADMIUM IN HUMANS

Attempts to quantify the health impact of cadmium on man with regard to its potential effect on the United States population as a whole are discussed in this portion of the report. The discussion leans heavily on empirical data and theoretical approaches. The main concern will be with chronic exposure situations.

4.4.1 Dose Aspects

Dose, as defined on page 4-3, is taken to mean that amount of cadmium derived from either external or internal exposure.

The general population of the United States, as elsewhere, receives its major external exposure to cadmium via inhalation and ingestion. While estimates of the dietary intake of cadmium in various countries cover a wide range of values, current estimates of median or average daily cadmium intake by ingestion in the United States generally range from 10 to 50 µg per day per person. Large segments of the general population are also exposed to additional burdens of cadmium via inhalation due to smoking (see 4.2, Exposure Aspects), since cigarettes contain notable amounts of cadmium. Exposure via ambient air, however, appears to be relatively negligible for the general population, except for persons living in close proximity to certain cadmium-emitting point sources. Exposure to cadmium via drinking water also generally represents a negligible input for the general population.

The relative values of various biological materials as internal indices of cadmium exposure have been reviewed (Friberg et al., 1974; Nordberg, 1976). As noted in the metabolism section, blood levels of cadmium after administration to animals show a kinetic profile that includes rather rapid clearance followed by a slow rise, mirroring hepatic uptake and incorporation into metallothionein followed by release into the blood stream. Blood-cadmium values are therefore of little utility in reflecting critical-organ exposure under chronic low-level exposure conditions.

Urinary cadmium levels are probably more relevant in assessing internal chronic exposure. The animal studies of Nordberg (1972a, 1972b) and the human-subject data of Tsuchiya (1972a, 1972b), Johnson et al. (1977), and Elinder et al. (1978) indicate that in the absence of impaired renal-tubular function there is a correlation between urinary cadmium levels and the main storage organs for the element. In addition, Nogawa et al. (1979) demonstrated a close relationship between cadmium concentrations in urine, when expressed in terms of μg/g creatinine, and such indices of renal tubular dysfunction as proteinuria.

Hair-cadmium levels have not been shown to reflect well body burdens of cadmium and, as such, do not presently appear to be a useful exposure indicator.

4.4.2 Dose-Effect/Dose-Response Aspects

Various adverse health effects that have been associated with cadmium exposure were described extensively in Chapter 2 and summarized in Section 4.3 of the present chapter. In those previous discussions, the central focus was on qualitative characterization of pertinent health effects rather than a thorough quantitative assessment of relationships between cadmium exposure levels and associated pathophysiological outcomes. The present section will deal with quantitative aspects of cadmium exposure and its effects on health. In that regard, two main types of relationships must be considered: dose-effect and dose-response relationships.

Pfitzer (1976) drew the distinction between effect and response in the following terms: "Effect" is taken to indicate the variable change due to a dose in a specific subject, and "response" is the number of individuals showing that effect, i.e., the number of "reactors" and "non-reactors" to the defined dose and specific effect in a group.

The kidney (kidney cortex) is generally accepted as being the critical organ for the chronic-exposure effect of cadmium; it is therefore appropriate to discuss data that define relationships between cadmium exposure and the effects of cadmium on renal function. In particular, proteinuria is typically taken as the main biochemical index of renal dysfunction induced by cadmium.

As for indices of cadmium exposure, blood cadmium levels cannot be used to assess the status of the critical organ in terms of that organ's direct exposure to the insulting agent. Urinary cadmium is a better index of overall cadmium exposure, but it is not a sufficiently good indicator of the extent of functional damage to the kidney to allow it to be a useful long-term diagnostic indicator of health impairment. Rather, the accumulation of cadmium in the kidney itself is presently generally accepted to be the best index of long-term cadmium exposure visa vis the definition of critical dose level(s) for induction of renal damage. Substantial attempts have, therefore, been made to define an approximate critical concentration of cadmium in the human kidney (kidney cortex) above which renal dysfunction can be expected to occur.

In regard to the definition of a critical concentration of cadmium in the kidney necessary for the induction of renal dysfunction, a range of estimates has been reported by different investigators. For example, as discussed in Chapter 2 of the present document, studies on the rat by Kawai and coworkers (Kawai and Fakuda, 1974; Kawai et al., 1974) found renal tubular atrophy and other morphological signs of kidney damage to be associated with a kidney cadmium concentration of 150 µg/g wet weight. In addition, Nomiyama (1975) reported increased protein excretion in rabbits as occurring starting at an average kidney cadmium concentration of 200 µg/g wet weight, and Suzuki (1974) observed proteinuria and increased urinary cadmium excretion at an average kidney cadmium cortex concentration of 225 µg/g wet weight.

Based on animal data of the above type and certain human autopsy data, Friberg et al. (1974) have proposed that 200 µg/g wet weight of kidney cortex be considered as the critical concentration for cadmium-induced renal dysfunction, as indexed by proteinuria; and WHO (1977) and the Subcommittee on the

Toxicology of Metals under the Permanent Commission and International Association of Occupational Health have tentatively endorsed this proposal (CEC, 1978). It should be noted that the WHO (1977), while endorsing the 200 μg/g critical concentration as the best estimate, also pointed out that the critical concentration could range from 100 to 300 μg/g.

In contrast to the above groups, Nomiyama (1977) has suggested that 300 μg/g is the best estimate of the critical concentration of cadmium in kidney cortex. This is based on Nomiyama's assertion that estimates of the critical concentration are most appropriately derived from cases where proteinuria was the only pathological finding, so that renal cadmium concentration measurements are less likely to have been affected by possible reductions in renal cadmium levels from those present at the onset of renal dysfunction. Such reductions in renal concentrations are known to occur due to increased outflow of kidney cadmium that commences after the onset of renal tubular damage. Nomiyama (1977) noted that, from among the eight human autopsy cases upon which Friberg et al. (1974) based their 200 μg/g proposal, those manifesting proteinuria only had renal cortex cadmium concentrations ranging from 21 to 395 μg/g wet weight, with all but one being at least 150 μg/g and four exceeding 300 μg/g. On this basis and other supporting data derived from studies on monkeys (Nomiyama, 1977), Nomiyama suggested that 300 μg/g may be a more accurate estimate than 200 μg/g for the critical concentration of cadmium in renal cortex necessary for the induction of renal dysfunction. On the other hand, other investigators (Brown _et_ _al_., 1978) have countered Nomiyama's comments by suggesting that 50 μg/g should be taken as being the critical concentration in the absence of more conclusive evidence for a "no-effect" level existing below 100 μg/g.

Regardless of whether 50, 200, or 300 μg/g is taken as being the best estimate of a theoretical critical concentration, it should be remembered that a "typical" threshold cadmium concentration necessary to induce renal dysfunction is implied by each estimate. No single estimate, however, can fully reflect the wide range of individual biological variation that has been observed to exist for induction of renal dysfunction in both human and animal studies. Nevertheless, taking a specific single value designated as being the best estimate of the "critical concentration," it is possible through the use of metabolic models to estimate probable levels of cadmium exposure sufficient to produce that critical concentration in the renal cortex. In that regard, several such metabolic models have been developed using 200 μg/g (wet weight) in kidney cortex as the critical concentration, in view of the 200 μg/g value being the presently most widely accepted estimate (WHO, 1977; CEC, 1978).

The theoretical basis for such modeling is: if the critical concentration of cadmium in the renal cortex is defined as the dose level at which renal dysfunction effects begin to occur in the most sensitive segment of the population, then limiting doses (exposures) to levels which produce values less than that in the kidney cortex should be sufficient to protect the entire population.

Some results obtained with metabolic models, as reported by Friberg _et_ _al_. (1974), Nordberg (1974), and Kjellström (Kjellström, 1976), are summarized in Table 4-12. Two types of calculations are presented in the table, those pertaining to the absorbed doses necessary to achieve a kidney cortex concentration of 200 μg/g and those pertaining to corresponding exposures necessary to achieve that concentration. All calculations are made for two estimates of biologic half-time for cadmium: 18- and 38-years. For a 50-year exposure, a

Table 4-12. CADMIUM EXPOSURE REQUIRED FOR REACHING A KIDNEY CORTEX CONCENTRATION OF 200 μg Cd/g USING DIFFERENT ALTERNATIVES FOR BIOLOGICAL HALF-TIME IN KIDNEY CORTEX AND EXPOSURE TIME[a]

Basis of calculation[b]		Exposure time (yr)	Levels of cadmium retention or exposure yielding renal dysfunction, assuming cadmium half-times of: 38 yr	18 yr
			Daily retention (μg)	
Constant daily retention during whole exposure time		10	36	39
		25	16	20
		50	10	13
			Industrial air concentration (in μg/m^3) yielding renal dysfunction	
25% pulmonary absorption, 10 m^3 inhaled per work day, 225 work days/year		10	23	25
		25	11	13
			Daily cadmium intake (μg)	
Food exposure for 50-yr-old person (2500 ca/day) (4.5% retention) (changing caloric intake by age accounted for)		50	250	360
			Corresponding average Cd concentration in foodstuffs (μg/g)	
Total amount (net weight) of food/day	300 g	50	0.8	1.2
	600 g		0.4	0.6
	1000 g		0.25	0.35

[a] Adapted from Friberg, L. M. Piscator, G. G. Nordberg, and T. Kjellström. Cadmium in the Environment. CRC Press, Cleveland, 1974.

[b] Assumptions: one-third of whole body retention reached kidney and kidney cortex concentration 50% higher than average kidney concentration. From Nordberg, G. F. (ed.). Effects and Dose-Response Relationships of Heavy Metals. Elsevier, Amsterdam, 1976.

daily retention of 10 μg/day would be sufficient, assuming the 38-year estimate of biologic half-time, to achieve the two hundred microgram per gram (200 μg/g) level in the kidney cortex. The corresponding retention figure of 13 μg/day applies if a half-life of 18 years is assumed. Thus an effect of estimated biological half-time on estimated retained cadmium necessary to reach the critical concentration in the kidney cortex is readily apparent, but this effect is relatively small in comparison to that of exposure duration.

The remainder of the table demonstrates the effect of exposure duration and biological half-time on the daily exposures necessary to achieve the critical concentration in the cortex. For a person occupationally exposed to cadmium, and assuming a half-life of 38 years, only 25 years of exposure to an air cadmium concentration of 11 $\mu g/m^3$ would be necessary for the critical value to be reached. Also, given the assumptions listed in the table, a daily dietary intake of 250 to 360 μg of cadmium would be sufficient over a 50-year exposure period for the critical concentration to be reached.

The above modeling approaches, however, have limitations as pointed out by Nordberg (1976) and in order to assess their validity, it is obviously necessary to evaluate the correspondence of results predicted by a given model to actual observed data. That is, it would be useful to compare predicted and actual exposure values for inhalation of amounts of cadmium resulting in increased incidence of proteinuria in occupationally exposed workers or for ingestion of foodstuffs of known cadmium content in population groups showing evidence (proteinuria) of renal dysfunction.

Kjellström (1976) has complied data which relates estimated airborne cadmium exposure of workmen to observed incidence of proteinuria; and it appears that the incidence of proteinuria is significantly elevated in workmen after 10 to 20 years of workplace exposure to air cadmium levels as low as 50 μg/m^3. This is within a factor of two of predicted levels listed in Table 4-12 for industrial air concentrations (23-25 μg/m^3) likely to result in the critical concentration being reached in kidney cortex after 10 years of exposure. It is interesting to contrast the predicted levels of air exposure yielding signs (e.g., proteinuria) of renal dysfunction as the "critical effect" of cadmium exposure in comparison to air values estimated to cause more acute toxic effects of cadmium. Friberg et al. (1974), for example, concluded that in man lethal, acute exposure to a cadmium level in air is approximately 5 mg/m^3 (5000 μg/m^3) for an 8-hr period, whereas emphysema, a chronic respiratory effect, generally starts to occur when the air level value is about 0.1 mg/m^3 (100 μg/m^3) and probably lower (66 μg/m^3) in the case of workers who smoke (Lauwerys et al., 1974).

Kjellström (1976) also evaluated epidemiological studies on the occurrence of proteinuria in Japanese populations residing in identified, high-cadmium-exposure areas. The data from these studies are valuable in that, in most cases, the exposure was dietary and several studies measured the cadmium level of the chief dietary component. The results obtained correspond well with dietary cadmium intake estimates of 250 to 360 μg/day based on the above metabolic model. Consistent with Kjellström's (1976) findings, a WHO working group (WHO, 1977) analyzed epidemiological data from Japan and concluded that an average daily dietary intake of 300-480 μg would cause the critical level for renal dysfunction to be reached. Lower levels of daily dietary cadmium intake, however, would presumably be sufficient for the critical renal cortex concentration to be reached in the most susceptible members of the population and, as such, would more closely approximate "threshold" levels of dietary cadmium intake associated with cadmium-induced renal dysfunction in sensitive members of exposed populations.

In that regard, a scientific group more recently evaluating dose-response relationships for cadmium (i.e., The Working Group of Experts for the Commission of European Communities) has estimated the threshold effect level for cadmium by ingestion to be around 200 μg daily, corresponding to an actual absorption of 12 μg/day, over a 45- to 50-year exposure period (Criteria - Dose/Effect Relationships for Cadmium, 1978). For smokers this estimate is reduced by about 1.9 μg to 10.1 μg, which corresponds to an oral intake of 169 μg/day. Using a second approach, also based on metabolic modeling of the above type, this same group derived a projected threshold effect level of 248 μg daily for dietary cadmium intake, when pulmonary absorption is negligible.

Thus far, in the present discussion of dose-effect and dose-response relationships, we have focused on various modeling approaches used to define dose-effect relationships. Such approaches, as seen above, both seek to define a critical concentration of cadmium in the kidney for the induction of renal dysfunction and, also, "average" or "threshold" external exposure values for either inhalation or ingestion of cadmium that will result, over long periods of time (10, 25, 50 years), in the critical concentration for renal dysfunction being reached. They are useful in helping to conceptualize dose-effect relationships for cadmium-induced renal damage in that: (1) they provide a theoretical framework within which complex interrelationships between external exposure doses (via inhalation or ingestion), internal exposure levels (as indexed by renal cadmium levels), and consequent renal dysfunction (indexed by proteinuria) can be stated in a simplified manner; (2) also, as such, they provide one means for trying to predict critical levels of external exposures that would result in the induction of renal damage in humans; and (3) they allow for empirical verification of their accuracy in terms of comparison of predicted versus observed values for pertinent parameters.

The above types of modeling approaches, however, have their limitations, as noted earlier, and should be viewed visa vis their utility within the context of what their limitations allow. Among the more crucial points to be remembered is that such models do not allow for one to adequately take into account individual biological variation in regard to the relationships characterized by the models. For example, in calculating external exposure levels necessary for reaching a certain renal cadmium concentration, average absorption or retention rates for cadmium intake via inhalation or ingestion are used. Specific individuals, however, it should be emphasized, have absorption or retention rates that vary from the average, some being much lower and others much higher. Thus, a given external exposure level may produce a relatively low renal cadmium accumulation in one person while the same exposure level can result in a much higher renal accumulation in another individual. Similarly, certain renal accumulations could be associated with renal dysfunction for the most susceptable members of a human population at levels distinctly lower than those producing such damage "on the average."

Based on the above considerations, it is therefore conceivable that a relatively low external exposure level could result in a renal cadmium accumulation for one individual distinctly above the average for a group; and, also, that renal accumulation, while low in comparison to the average level necessary to induce renal dysfunction, could nevertheless result in significant renal dysfunction for the given individual. Conversely, some individuals, the least susceptable ones in a population, may not experience renal dysfunction even at exposure levels much higher than the average level yielding such damage for most members of the population. The existence of wide variability in individual dose-effect relationships for cadmium-induced renal effects is hinted at, for example, by the range of renal cortex cadmium concentrations (21 to 395 µg/g wet weight) reported by Friberg et al. (1974) to be associated with proteinuria, as discussed earlier. It is important, therefore, in any risk assessment for cadmium-induced renal damage to take into account such individual variability and to consider what proportion of a target population will show signs of renal dysfunction at various cadmium exposure levels. Some initial progress in attempting to defining such dose-response relationships has been accomplished recently (Kjellström, 1977a, 1978; Kjellström and Nordberg, 1978, Nogowa et al, 1978).

Kjellström (1977, 1978) and Kjellström and Nordberg (1978) reported on a more elaborate metabolic model developed by them in order to overcome some of the uncertainties associated with earlier modeling attempts, especially in regard to better taking into account individual biological variation in the accumulation of cadmium in kidney cortex and the induction of renal effects. Using both calculated and epidemiological cadmium exposure and retention data, and renal tubular dysfunction prevalence indexed by β_2-microglobulin excretion as the adverse health effect, complex dose-response relationships for cadmium renal effects in man were modeled by Kjellström and Nordberg. In Figure 4-5 are depicted calculated (lines) and observed (symbols) dose-response relationships for cadmium-induced increase of urinary β_2-microglobulin excretion. The abscissa expresses exposure as daily intake of cadmium multiplied by an assumed 50-year period of exposure, while the ordinate shows both percent population affected and the corresponding probits. The numerical

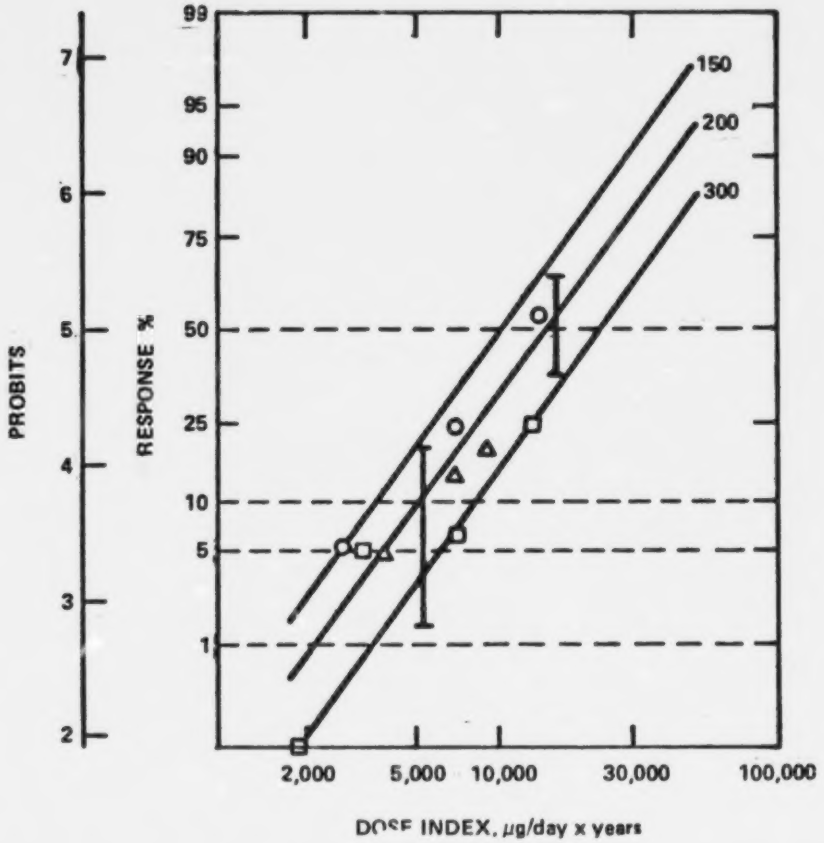


Figure 4-5. Calculated (lines) and observed (symbols O, □, △) dose-response relationships for cadmium-induced increase (> 97.5 percentile of reference group) of urinary β_2-micro-globulin excretion.

Source: Kjellström (1977).

values besides the lines are for three renal cortex "critical concentration" cadmium values: 150, 200, and 300 µg/g net weight. The actual, or observed, response rates indicated by symbols fit well within the predicted values derived from the model.

The Kjellström model predictions take into account the varying kidney and body sizes of Europeans and Japanese and represent values for response rates at age 50. Note that 440 µg/day is the average (median) level of intake projected to result in renal dysfunction for non-smoking adult Europeans (or Americans based on equivalent body size). At a dietary intake level as low as 60 µg/day, however, average-sized adult Americans are predicted to show a 1.0 percent response rate and, by 100 µg/day and 150 g/day, approximately 5 and 10 percent would be predicted to exhibit renal proteinuria as indexed by increased β_2-microglobulin excretion. These latter response rates are, of course, distinctly higher than the near-zero rates at those intake levels implied by the above CEC calculations of "threshold" critical dietary intake levels of *ca*. 200 µg/day. As Kjellström has noted (Kjellström, 1977, 1978), however, dose-response relationships defined by his model are based on a number of assumptions which must be viewed with caution.

In regard to some of the more salient points of caution concerning the Kjellström predictions, it should be noted that agreement between predicted and observed values is best at levels above 100 µg/day where the largest numbers of observed data points pertain. However, extrapolating these estimates in a linear, non-threshold fashion to lower exposure levels (e.g., 30-60 µg/day) does not appear to be presently well-justified in the absence of observed health data at the lower exposure levels. Further questions can also be raised concerning the interpretation of the renal proteinuria prevalence rates projected to occur at levels below 100-150 µg/day.

That is, in his thesis, Kjellström cites observed response rates for control populations (β-microglobulin levels above his operational definition for damage) of 3.4 percent for Sweden, and 2.5 to 3.2 percent for Japanese (Kjellström, 1977). With such background prevalence rates, which likely involve many many other etiological factors producing proteinuria, the significance of percentages less than 5 percent being attributed to cadmium is somewhat unclear. A related factor bearing on this point and further complicating matters is the fact that Kjellström (1977) defined excessive β-microglobulin excretion as that exceeding 290 μg/l, i.e., the 95 percent confidence level based on a geometric average excretion of 84 μg/l for normal unexposed persons. Therefore, by definition, there should be a 2.5 percent response rate in the unexposed population.

The Kjellström model is also deterministic and has no standard deviation around the 440 μg Cd/day average intake associated with it. To accomplish his purpose, Kjellström derived a geometric standard deviation of 2.35 from studies of autopsied tissue (Kjellström, 1977). The units of the 2.35 value are in μg Cd/g kidney cortex (Elinder et al., 1976). However, Kjellström then applied a log normal distribution with geometric standard deviation of 2.35 around the 440 average food intake value. The food intake has units of μg/day. His assumption that the same standard deviation applies to kidney cadmium concentration and daily food intake is debatable and results in much uncertainty surrounding the accuracy of his model projections, especially at exposure levels at increasing distances from the 440 μg/day average.

Nogawa et al. (1978) also present data on cadmium induced renal dysfunction which may be used to define dose-response relationships; in this case excretion of retinol binding protein (RBP > 4 mg/l) was used to define renal tubular proteinuria. Data on cadmium in rice and RBP in urine (Table 4-13) showed a consistent increase in prevalence of renal tubular proteinuria among inhabitants over 50 years of age to be associated with every rice cadmium concentration category exceeding levels (ca. 0.20 μg/g) observed for rice consumed by the control village inhabitants. Thus, at cadmium levels as low as 0.19 to 0.29 μg/g of rice, statistically significant increases in prevalence of tubular proteinuria over that seen with control levels of cadmium in rice appear to occur for Japanese individuals over 50 years of age. Dietary rice levels of 0.19 to 0.29 μg/g can be estimated to result in an equivalent total dietary cadmium intake of 96 to 147 μg/day, based on assumptions and calculations reported by Ryan (1978). Corrected for differences in body size, these levels would be equivalent to approximately 150-200 μg/day intake for Europeans/Americans. The Nogawa data are presented on a more detailed age-related basis in Table 4-14.

In summary, best estimates derived from the above data indicate that renal tubular dysfunction, as indexed by proteinuria, is induced when kidney cortex cadmium levels reach a critical concentration of approximately 200 μg/g wet weight. Also, based on metabolic modeling results and empirical observations, it appears that the critical renal cortex cadmium concentration is not usually reached as a consequence of dietary cadmium intake (the main source of exposure for the general public), unless such intake levels exceed 150-200 μg/day over a 50-year exposure period. In order to accurately estimate the likely risk for the general population associated with either airborne or water cadmium exposures, one must take into account the above facts and other information presented below on populations at risk so that overall multimedia contributions to human cadmium exposure in various situations can be considered.

Table 4-13. PREVALENCE OF TUBULAR PROTEINURIA AND SUSPECTED PATIENTS AMONG ADULTS MORE THAN 50 YEARS OF AGE IN RELATION TO VILLAGE AVERAGE RICE CADMIUM CONCENTRATIONS

Village average rice cadmium concentration (μg/g)			Urinary excretion of retinol binding protein				
			Greater than (±)[b] (percent)	Greater than ±[c] (percent)	Greater than +[d] (percent)	Suspected patient (percent)	Tubular proteinuria, amino aciduria[e] and decreased TRP%[f] (percent)
Polluted village	Mean	N[a]					
0.19 - 0.29	(0.24)	1122	4.55*	3.39*	1.52	1.25	0.27
0.30 - 0.39	(0.38)	413	7.02**	4.84**	2.66*	2.66**	0.24
0.40 - 0.49	(0.45)	616	5.84**	4.22**	2.76**	3.25**	0.97
0.50 - 0.59	(0.56)	353	13.03**	11.61**	8.50**	6.80**	1.98*
0.60 0.69	(0.65)	140	30.00**	24.29**	14.29**	12.1**	5.71**
Control		248	1.21	0.81	0.40	0	0

[a] Number of persons examined.
[b] Around 4 mg/liter.
[c] Around 8 mg/liter.
[d] Around 16 mg/liter.
[e] Proline; more than 10 mg/liter. Amino N; more than 300 mg/g creatinine.
[f] Less than 80 TRP%.
* Significant difference ($P<0.05$) compared with control.
** Significant difference ($P<0.01$) compared with control.

Source: Nogawa et al. (1978)

Table 4-14. PREVALENCE OF TUBULAR PROTEINURIA IN RELATION TO AGE AND VILLAGE AVERAGE RICE CADMIUM CONCENTRATION

Age	Greater than RBP (±)						Greater than RBP (+)					
Cd in rice	50 - 59		60 - 69		≥70		50 - 59		60 -69		≥70	
(microgram per gram)	N[a]	Percent	N[a]	Percent	N[a]	Percent	N[a]	Percent	N[a]	Percent	N[a]	Percent
Control	104	0.96	80	2.50	64	0.00	104	0.00	80	1.25	64	0.00
0.19 - 0.29	477	0.84	377	2.65	268	13.81**	477	0.42	377	0.80	268	4.48
0.30 - 0.39	184	3.26	138	5.07	91	17.58**	184	2.72	138	0.72	91	7.69*
0.40 - 0.49	295	1.69	204	6.86	117	14.53**	295	0.34	204	2.94	117	8.55**
0.50 - 0.59	140	0.71	120	10.83*	93	34.41**	140	0.00	120	5.00	93	25.81**
0.60 - 0.69	60	18.33**	57	24.56**	23	73.91**	60	5.00*	57	12.28**	23	43.48**

[a] Number of persons examined.

* Significant difference ($P<0.05$) compared with control.

** Significant difference ($P<0.01$) compared with control.

Source: Nogawa et al. (1978)

4.5 POPULATIONS AT RISK TO EFFECTS OF CADMIUM

Population at risk is that segment of a defined population exhibiting characteristics associated with a significantly higher probability of developing a condition, illness, or other abnormal status. This higher risk may result from either greater inherent susceptibility or from exposure situations peculiar to that group. Inherent susceptibility refers to some host characteristic or status which predisposes that host to a heightened response to an external stimulus or agent.

The collective Japanese experience with water- and airborne cadmium pollution can be cited as one example where many factors placing particular groups at risk for cadmium-induced renal damage have been identified. Working back from demonstrated heightened vulnerability in Japanese subgroups of populations may therefore allow American populations at risk to be identified as well.

Japan is, to date, the only known location where cadmium exposure was/is high enough to affect significant groups of the regional population in those areas of cadmium pollution via water and/or air. In the Japanese experience with cadmium, the clinical extreme of which is Itai-Itai disease, the individuals found to be most vulnerable to the effects of cadmium were post-menopausal women with a history of multiple childbirths as well as calcium and Vitamin-D deficiency. This hints, in part, at women in general possibly being at special risk and also seems to point to nutritional status as being an important determinant in placing certain groups at special risk for the adverse health effects of cadmium.

In addition to the above, a consistent finding in most of the cadmium-polluted areas of Japan has been the factor of age as a determinant in the prevalence of proteinuria, a measure of renal dysfunction, with proteinuria being observed most often in groups above 40 years of age. Thus, older members of any population appear to be more at risk in any demonstrated or potential cadmium-exposure setting, with those having nutritional deficits exhibiting the highest risk.

Perhaps even more importantly for present purposes, however, given that the gradual accumulation of cadmium in the renal cortex over a long period of time (e.g., 20 to 50 years) is a key factor in inducing renal dysfunction in humans, then the entire population must be considered as being at potential risk for such effects over their lifetimes. Thus, as a starting point, current dose-response relationships for the United States population in general must be defined. Then, particular groups at special risk beyond that existing for the general population need to be delineated.

In order to assess the potential impact of various cadmium exposure situations on the health of the United States population, a dose-response model must be derived which relates existing American cadmium exposure levels to predicted response rates for renal dysfunction. Of greatest importance here are considerations of dietary cadmium intake as the single most important source of cadmium exposure for the general United States population. In regard to estimates of current daily dietary cadmium intake for Americans, it was earlier (Section 4.2.4) noted that somewhat different ranges of estimates have been arrived at by the FDA via food survey studies than those obtained through EPA-sponsored fecal excretion studies (Table 4-8). The collective results of the latter studies, accepted here as likely being the more accurate estimates of current American dietary cadmium intake levels, indicate that most (>50.0 percent) of Americans ingest less than 20 μg of cadmium per day; a small proportion of the population (~1.0 percent), however, appear to exceed 50 μg/day of dietary cadmium intake.

It was also noted earlier (Section 4.4.2) that several different approaches have been used for estimating dietary intake levels expected to result in a critical renal cortex cadmium concentration associated with renal dysfunction being reached over a 50-year exposure period. Using certain metabolic model approaches, estimates ranging from 200 to 480 μg/day have been generated for nonsmokers; however, values at the lower end of that range, i.e., 200 to 248 μg/day, have been accepted as the best estimates by a Working Group of Experts for the Committee of European Communities (CEC, 1978). These calculations comport well with the estimates of 150-200 μg/day that can be derived from Nogowa et al. (1978) observed dose-response data for Japanese populations exposed to cadmium via dietary intake. If the above estimates are accurate, then current American dietary intake levels of 10 to 50 μg/day would appear to be distinctly lower than levels yielding critical renal cortex cadmium concentrations associated with renal dysfunction. On the other hand, certain other presently available information suggests that such a large gap between current intake levels and those producing renal dysfunction may not exist for the most susceptible members of the United States population.

More specifically, as discussed earlier under Section 4.4.2, Kjellström's (1977) modeling of predicted dose-response relationships suggests that as many as 1 percent of the American population could exhibit signs (proteinuria) of renal tubular damage at a daily dietary cadmium intake level of 60 μg/day. The same model predicts expected response rates of 2.5 percent and 5 percent at dietary intake levels of 80 and 100 μg/day, respectively. Viewed from this latter perspective, then, current estimated United States dietary intake levels of 10 to 50 µg/day would range from being less than two to about eight times less than intake levels yielding renal dysfunction for small portions of the general population as a consequence of 50 years of dietary cadmium exposure. The accuracy of these latter Kjellström model projections, however, can be disputed based on factors discussed above; therefore, their use at this time for risk assessment purposes is not advised.

All of the above information collectively suggests that few members, if any, of the general (non-smoking) American population have daily dietary cadmium ingestion levels that approach those likely to yield renal tubular dysfunction in old age (i.e., after a 50-year exposure period). However, in addition to dietary intake as an element of risk potentially present for the general United States population, a distinctly higher level of risk for cadmium-induced renal dysfunction has been rather conclusively shown to exist for individuals that smoke cigarettes.

In an earlier portion of this Risk Assessment section (Exposure Aspects, 4.2) the relative contribution of smoking to daily cadmium retention as a function of increasing cigarette use was tabulated. In Table 4-15, significant increments in daily retained amounts (daily increase in burden) of cadmium can be seen to arise from cigarette smoking, the relative values being particularly striking if one takes 25 µg/day as the average intake arising from food. Assuming a daily intake of 25 µg, smoking one, two, or three packs of cigarettes a day furnishes percentages of 41, 58, and 63 percent, respectively, of daily cadmium retention for smokers. Even in the case where 50 µg/day is the dietary

TABLE 4-15. RELATIVE CONTRIBUTION OF CIGARETTE SMOKING TO TOTAL DAILY CADMIUM RETENTION[a]

Cigarette packs/day	Daily food intake of 50 μg	25 μg
0	0%	0%
1/2	17%	26%
1	29%	41%
2	45%	58%
3	55%	63%

[a] Daily cadmium retention for water and air 0.51 μg total. (See Table 4-11).

intake of cadmium, the smoking of two packs of cigarettes daily roughly doubles the daily total retention. In Table 4-16 are given the relative contributions of smoking to total daily cadmium intake as a function of different ambient air levels and varying dietary intake levels (25, 50 and 75 µg/day) reflecting current and possibly increased future dietary intake levels in the United States.

If one now relates these values to the table (Table 4-12) containing figures for the estimated level of daily retention of cadmium as a function of exposure time (first part of Table 4-12), above which the critical concentration for renal dysfunction is reached at the end of the exposure period, a definite increase in risk for non-smokers to reach the critical retention limits (10-13 µg/day) becomes apparent as air levels increase from 100 to 1000 $\mu g/m^3$, even assuming only the two lowest dietary intake levels. A much greater incremental risk for heavy smokers is evident even at air concentration levels as low as 100 $\mu g/m^3$. For example, in the case of a daily intake of 50 µg cadmium in food (3.0 µg/day net retention), an individual smoking two or three packs of cigarettes per day throughout his adult lifetime approaches two-thirds of the critical retention level (10-13 µg/day) at age 70, assuming smoking started at age 20 and <10 ng/m^3 ambient air cadmium exposure. At higher chronic ambient air exposure levels, i.e., at 100-1000 ng/m^3, heavy smokers would be expected to closely approach or exceed cadmium retention levels resulting in renal tubular dysfunction.

In assessing the potential impact of ambient air cadmium exposures, if one tabulates the relative contributions of ambient air cadmium over the range of 1 to 1,000 ng/m^3, taking into account cadmium retention from dietary intake and cigarette consumption, one arrives at the figures in Table 4-17. At

Table 4-16. ESTIMATED RELATIVE CONTRIBUTION OF DIETARY INTAKE, CIGARETTE SMOKING AND AMBIENT AIR CADMIUM LEVELS TO TOTAL DAILY CADMIUM RETENTION FROM ALL SOURCES[a]

Dietary Intake (Net Retention)	Smoking Status (Net Retention)	Air Cadmium Levels (Net Retention) 0.0 ng/m^3 (0.0 µg/day)	1.0 ng/m^3 (.005 µg/day)	10 ng/m^3 (.05 µg/day)	100 ng/m^3 (.50 µg/day)	1000 ng/m^3 (5.0 µg/day)
Food Level A = 25 µg/day (1.50 µg/day)	Non-smoker (0.00 µg/day)	1.590 (0;0%)*	1.595 (0;0%)*	1.640 (0;3%)	2.090 (0;25%)	6.590 (0;76%)
	½ pack/day (0.70 µg/day)	2.290 (31;0%)	2.295 (31;0%)	2.340 (30;3%)	2.790 (25;18%)	7.290 (10;68%)
	1 pack/day (1.41 µg/day)	3.000 (47;0%)	3.005 (47;0%)	3.050 (46;2%)	3.500 (40;14%)	8.000 (18;63%)
	2 pack/day (2.82 µg/day)	4.410 (64;0%)	4.415 (64;0%)	4.460 (63;1%)	4.910 (57;10%)	9.410 (30;53%)
	3 pack/day (4.22 µg/day)	5.810 (73;0%)	5.815 (72;0%)	5.860 (72;1%)	6.310 (67;8%)	10.810 (39;46%)
Food Level B = 50 µg/day (3.00 µg/day)	Non-smoker (0.00 µg/day)	3.090 (0;0%)	3.095 (0;0%)	3.140 (0;2%)	3.590 (0;14%)	8.090 (0;62%)
	½ pack/day (0.70 µg/day)	3.790 (18;0%)	3.795 (18;0%)	3.840 (18;1%)	4.290 (16;12%)	8.790 (8;57%)
	1 pack/day (1.41 µg/day)	4.500 (31;0%)	4.505 (31;0%)	4.550 (31;1%)	5.000 (28;10%)	9.500 (15;15%)
	2 pack/day (2.82 µg/day)	5.910 (48;0%)	5.915 (48;0%)	5.960 (48;1%)	6.410 (44;8%)	10.910 (26;46%)
	3 pack/day (4.22 µg/day)	7.310 (58;0%)	7.315 (57;0%)	7.360 (57;1%)	7.810 (53;6%)	12.310 (34;41%)
Food Level C = 75 µg/day (4.50 µg/day)	Non-smoker (0.00 µg/day)	4.590 (0;0%)	4.595 (0.0%)	4.640 (0;1%)	5.090 (0;10%)	9.590 (0;52%)
	½ pack/day (0.70 µg/day)	5.290 (13;0%)	5.295 (13;0%)	5.340 (13;1%)	5.790 (12;9%)	10.290 (7;49%)
	1 pack/day (1.41 µg/day)	6.000 (24;0%)	6.005 (23;0%)	6.050 (23;1%)	6.500 (22;8%)	11.000 (13;46%)
	2 pack/day (2.82 µg/day)	7.410 (38;0%)	7.415 (38;0%)	7.460 (38;1%)	7.910 (36;6%)	12.410 (23;40%)
	3 pack/day (4.22 µg/day)	8.810 (48;0%)	8.815 (48;0%)	8.860 (48;1%)	9.310 (45;5%)	13.810 (31;36%)

*Each first value equals total daily cadmium retention levels (in µg/day) from all sources, assuming constant daily retention from water of 0.09 µg/day derived from consumption of water with cadmium concentration of 1 ppb. The two values in parentheses ( ) indicate percentage of total daily cadmium retention attributed to cigarette smoking and ambient air cadmium exposure, respectively, at a given ambient air cadmium level.

[a] Note that daily cadmium retention of 10 µg/day would be projected to result in a critical cadmium concentration of 200 µg/g wet weight of kidney cortex being reached over a 50-year exposure period, assuming a kidney half-time for cadmium of 38 years. A comparable value of approximately 13 µg/day of cadmium retention obtains if a kidney half-time for cadmium of 18 years is assumed.

ambient air levels of 1 and 10 ng/m^3, no air contribution is made that significantly enhances the risk of smokers over that arising from diet and cigarettes. At levels of 100 ng/m^3, however, a uniform increase of 5 percent is seen, with the increase in percentage at 1,000 ng/m^3 being about 50 percent over that of no ambient air levels of cadmium.

Experimental data in support of considering smokers as being at increased risk for the renal effects of cadmium are available from human autopsy studies of organ cadmium levels, particularly kidney cadmium levels. These studies are described in the Human Epidemiology section and show that smokers have kidney levels of cadmium considerably above those for non-smokers, up to twice the relative amount.

In the Exposure Aspects portion of this chapter, mention is made of the growing use of sludge material dispersed on agricultural lands. Furthermore, it was pointed out that this material is often enriched in cadmium relative to soils in general and, therefore, its use may result in significantly increased cadmium levels in soil, food crops grown on the sewage-treated soil, and consumer-distributed food products derived from such crops. If this be the case, then one might project as a potential population at risk in the United States those who may be so placed at risk by virtue of dietary habits, in particular those for whom grains and leafy vegetables comprise the sole or major portion of their diet. These foodstuffs are particularly adept at taking up cadmium from soils.

Lucas _et_ _al_. (1978) have suggested that sludges with less than 60 ppm cadmium can be applied at maximum rates to meet crop nitrogen requirements and still produce acceptable levels of cadmium in vegetables, assuming 110 µg/day

TABLE 4-17. PERCENTAGE OF CRITICAL DAILY CADMIUM RETENTION LEVEL[a] YIELDING RENAL DYSFUNCTION ACHIEVED BY SMOKERS AS A FUNCTION OF AMBIENT AIR CADMIUM LEVELS[a,b]

		Ambient Air Concentrations (μg/m³)									
		0		1.0		10.0		100.0		1,000.0	
Cigarette packs/day	Daily food intake of:	25 μg	50 μg	25 μg	50 μg	25 μg	50 μg	25 μg	50 μg	25 μg	50 μg
0		19	34	19	34	19	34	24	39	69	84
1/2		26	41	26	41	26	41	31	46	76	91
1		33	48	33	48	33	48	38	53	83	98
2		47	61	47	62	47	62	52	67	97	112
3		61	76	61	76	61	76	66	81	111	126

[a] Assumed here to be 10 μg/day in calculating tabulated percentage values.

[b] Assuming daily cadmium retention from water of .36 μg/day.

[c] Exposure period of 50 years.

of cadmium ingestion via food to be safe. Factors which complicate any quantitative assessment of the risk impact of cadmium-containing sludge are population mobility and a centralized food marketing and distribution system that would have some diluting effect on high cadmium vegetables and grains. Still, increased dietary cadmium levels of any amount must be considered as further increasing the risk of population groups already at special risk, such as old people, vegetarians or smokers (as is illustrated for the latter in the bottom half of Table 4-16), and projected likely increases in dietary cadmium intake should be taken into account in estimating acceptable ambient air or water cadmium levels.

Scrutiny of the literature with reference to those individuals on the other end of the age scale, young children, furnishes very limited hard evidence of a clinical epidemiological nature that children may presently be considered a group at special risk for the health effects of cadmium. As implied in EPA's *Air Quality Criteria for Lead* (1977), however, children, by virtue of their relationship to their exposure setting may be at invariably greater risk for any toxic metal that parallels lead's distribution in the environment, particularly in dustfall. The "mouthing" activity of young children, a normal behavioral trait, would expose this group to non-foodstuffs such as cadmium-containing dust and dirt.

Bogden *et al*. (1974) studied the extent of exposure of a group of urban children to cadmium. These workers found a significant positive correlation between cadmium and lead ($p<0.006$) and between cadmium and zinc ($p<0.001$). These correlations suggest that, since increased lead concentrations in blood occur because of environmental contamination, then cadmium is being co-absorbed with the lead. While paint could be a source of both cadmium and lead, the zinc/cadmium correlation is more vexing as to source. As part of their study, they correlated the mean atmospheric concentrations of each element for a specific year and found strong positive correlations between the three pairs ($p<0.01$): cadmium/lead, zinc/lead and zinc/cadmium, indicating to these investigators that inhalation may be a factor in the blood values. Delves et al. (1973) in their study, however, could find a correlation of only 0.05 for lead and cadmium or between zinc and cadmium.

The hazard posed to children in this type of exposure setting may be heightened for several reasons:

(1) Many children in urban areas, particularly those of lower socio-economic status, have a greater incidence of calcium, iron, and zinc deficiency, which are states that could enhance the absorption and/or health effects of cadmium (see 2.16, Interactions section).

(2) Co-exposure of children to lead and cadmium may heighten the health effect of either or both through synergism.

(3) We know that industrial use of cadmium in urban areas adds to the dust and soil burden via fallout (see 4.2, Exposure Aspects) and to the exposure of children in these areas via "mouthing" activity, etc.

Another group within the general population of the United States who may be at increased risk are those whose water supplies are soft or acid. Soft water has been associated with heightened occurrence of cardiovascular disease (see 2.6 of the Health Effects section). While hypertension induced experimentally by cadmium has been established, at present the parallel data for humans do not conclusively show an etiological role for cadmium in human hypertension. This is an important issue and, like the case with children, requires more research.

The risk posed by cadmium to pregnant women, more specifically the fetus, is another area of concern. It has been shown, as described in the health effects section on reproduction and development, that although cadmium passes the placental barrier in only small amounts, it nevertheless can affect the birth weights and morphological development of offspring exposed _in utero_ through dosing of the mother. Such prenatal effects on fetal development also appear to persist into postnatal development and seem to occur secondarily to cadmium effects on the mother, e.g., in causing decreased levels of essential elements such as zinc, iron, and copper.

In light of the animal studies demonstrating such cadmium effects, the findings of Cvetkova (1970) on women in the U.S.S.R. occupationally exposed to cadmium oxide are quite interesting. Those women had normal courses of pregnancy and deliveries, but their children had lower birthweights when compared with those of control workers. Such results are consistent with those found in animal studies where reduced birthweight has been observed. Thus, there appears to be a reasonably well-established association between cadmium exposure during pregnancy and reduced birth weights. This adverse effect and a less well-demonstrated association with stillbirths argues for pregnant women being a special group at risk to cadmium by virtue of potential deleterious effects on the fetus. However, insufficient information currently exists to allow for accurate quantification of pertinent dose-effect or dose-response relationships.

Several studies provide further evidence for children continuing to be at risk well beyond the neonatal periods of their life. Higher than "normal" levels of cadmium have been demonstrated in children as a function of: (1)

increasing age (Delves et al., 1973; Gross et al., 1976) and (2) suspected pica and geographic location of residence, with inner-city children having higher levels than others (Bogden et al., 1974). The health implications of such cadmium exposures in children remain to be better established, however, as discussed elsewhere in the section on human epidemiology; but one must suspect that the general consequence would be that of putting them at higher risk for any of the many adverse health effects described earlier under the section on health effects.

4.6 UNITED STATES POPULATION GROUPS IN RELATION TO PROBABLE CADMIUM EXPOSURES

This section is concerned with the numbers of individuals potentially at risk to cadmium exposures. It is not possible to delineate well all of the members of those segments of the United States population that would fit the potential risk categories described in the previous section on populations at risk.

Table 4-18 presents estimates from EPA's Assessment of Human Exposures to Atmospheric Cadmium (1979) of the numbers of individuals in the U.S. population exposed to airborne cadmium levels >0.1 ng/m^3 as a function of average cadmium exposure and type of cadmium source. In terms of numbers of individuals exposed, those in proximity to municipal incinerators constitute the largest group and are exposed to a projected average annual air level of 8.4 ng/m^3 derived from the municipal incinerators. Iron and steel production result in the second largest group of individuals exposed, about 20 million. Comparatively smaller, but significant, populations are exposed to higher air levels ($\geq$10 ng/m^3), however, by virtue of residence near other high cadmium-emitting point sources, e.g., primary zinc, lead, and cadmium smelters. It should be noted, however, that the present numbers may underestimate actual annual exposures for some individuals in the vicinity of two or more different sources since the estimates in Table 4-18 do not take into account possible overlaps of exposure fields from different sources. This is most important for the municipal incinerators and iron and steel mills, which are often clustered in urban areas. Although large numbers of individuals are exposed via inputs from the above sources into the ambient air, the average exposure levels reported, except perhaps for those very close to high emitting point sources, generally do not appear to be associated with increased risk for any particular health effect. However, if the population estimates are broken down further according to more specific annual exposure concentrations for different source categories, as presented in Tables 4-19 to 4-22, then certain high risk exposure situations become more apparent when the listed air exposure concentrations are compared to those tabulated in Table 4-16. Note, for example, instances where population segments are exposed to greater than 100 $\mu g/m^3$ and expecially cases where exposures exceed 1000 ng/m^3.

Table 4-19 is a listing of numbers of persons exposed to different airborne cadmium concentrations arising from municipal incinerators. Also, Table 4-20 describes the numbers of individuals exposed to various air concentrations derived from iron and steel mills as another major source category. Table 4-21, on the other hand, depicts exposure populations by air concentrations derived from primary smelters, whereas Table 4-22 lists numbers of people exposed to varying air cadmium levels around secondary smelters. In addition, Figure 4-6 depicts the states included in the census regions employed in Tables 4-19 to 4-21, which contain tabulations of regional populations exposed to cadmium levels exceeding 0.1 nanograms Cd/m^3.

As noted earlier, smokers constitute a definite population at increased

TABLE 4-18. AVERAGE EXPOSURE AND NUMBER OF PEOPLE EXPOSED TO ANNUAL AIR CADMIUM LEVELS GREATER THAN 0.1 ng/m^3 BY SPECIFIED SOURCE TYPES[a]

	AVERAGE EXPOSURE		MAXIMUM EXPOSURE	
	Concentration (Annual Avg. ng/m^3)	Population (10^3 People)	Concentration (Annual Avg. ng/m^3)	Population (10^3 People)
Source				
Secondary Smelters				
Copper	1.51	9,891	>10	296
Zinc	0.5	37	0.1-1	37
Municipal Incinerators	8.4	48,270	>200	1.0
Primary Smelters				
Zinc[b]	86-110	376	>1,000	0.1-0.8
Lead[b]	9-11	105	100-1,000	0-0.2
Copper[b]	5.2-8.0	218-352	100-1,000	0-0.2
Cadmium[b]	3.0-15.0	150	>1,000	0-2.6
Iron and Steel	2	19,896	>10	372

[a] From EPA Assessment of Human Exposure to Cadmium (1979).

[b] Ranges result from differing assumptions concerning fugitive emissions; see text, Section 6.

TABLE 4-19. ESTIMATE OF CUMULATIVE POPULATION EXPOSED TO SPECIFIED CADMIUM CONCENTRATIONS FROM MUNICIPAL INCINERATORS[a]

(10^3 people)

Region	Annual Concentration (ng/m^3)				
	>200	>100	>50	>10	>0.1
1	1.0	3	14	612	6,470
2	0.0	0.5	1,016	1,655	16,730
3	0.0	0.1	53	679	8,567
4	0.0	0.0	22	40	2,935
5	0.0	0.0	250	650	12,144
6	0.0	0.0	7.7	7.7	1,098
7	0.0	0.0	38	81	157
8	0.0	0.0	4.6	4.6	169
9	-	-	-	-	-
10	-	-	-	-	-

[a] From EPA Assessment of Human Exposure to Cadmium (1979).

TABLE 4-20. ESTIMATE OF CUMULATIVE POPULATION EXPOSED TO SPECIFIED CADMIUM CONCENTRATONS FROM IRON AND STEEL MILLS[a]

(10^3 people)

	Annual Concentration (ng/m^3)			
Region	>10*	>5	>1	>0.1
1	0	0	0	93
2	0	49	470	1,649
3	52	137	1,965	4,543
4	177	341	578	1,610
5	143	339	1,852	8,710
6	0	29	521	1,575
7	0	0	23	108
8	0	24	176	224
9	0	15	161	774
10	0	0	33	833

*Maximum concentrations predicted around individual iron and steel mills may be as high as 30-40 ng/m^3.

[a] From EPA Assessment of Human Exposure to Cadmium (1979).

TABLE 4-21. ESTIMATED POPULATION EXPOSED TO SPECIFIED LEVELS FROM PRIMARY SMELTERS[a]
(10^3 people)

	Primary Copper Smelters					Primary Lead Smelters					Primary Cadmium Smelters					Primary Zinc Smelters				
	2% Fugitive Concentration (ng/m^3)					2% Fugitive Concentration (ng/m^3)					2% Fugitive Concentration (ng/m^3)					2% Fugitive Concentration (ng/m^3)				
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0.1	0.2	0.7	100.4	0.2	27.9	219.7	358.8	358.8
4	0	0	0	1.1	18.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0.1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0.1	3.6	0	0	0	0	0	0	0	0	0	32.4	0	0	0	0	0
7	0	0	0	0	0	0	0	0	1.5	59.8	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0.1	85.4	0	0	0	0.7	28.5	0	0	0	0	0	0	0	0	0	0
9	0	0	0.1	1.5	29.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0.1	1.3	122.0	0	0.1	0.4	13.8	17.4	0.1	0.2	0.4	1.6	17.2	0	5.9	17.2	17.2	17.2
TOTAL	0	0	0.2	4.2	261.0	0	0.1	0.4	16.0	105.7	0.1	0.3	0.6	2.3	150.0	0.2	33.8	236.9	376.0	376.0

[a] From EPA Assessment of Human Exposure to Cadmium (1979).

TABLE 4-22. ESTIMATE OF POPULATION EXPOSED TO SPECIFIED LEVELS FROM SECONDARY SMELTERS
(10^3 People)[a]

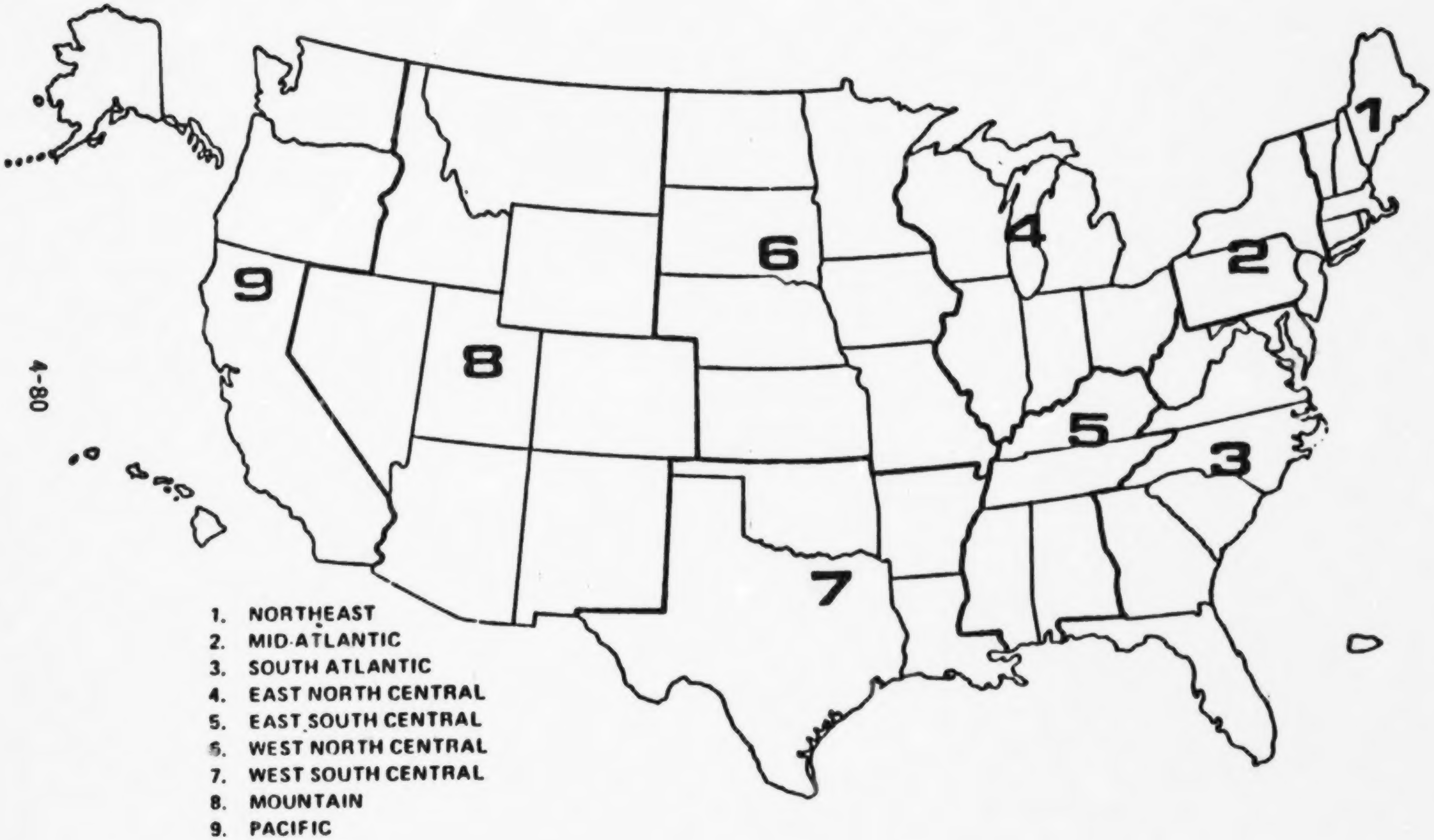
Smelter	Concentration (ng/m^3)				Annual Average Exposure
	>10*	>5	>1	>0.1	
Secondary Copper	296	798	5,710	9,891	1.5
Secondary Zinc	0	0	0	37	0.47

*Maximum concentrations around existing plants are estimated to be about 50 ng/m^3.

[a] From EPA Assessment of Human Exposure to Cadmium (1979).

risk for adverse health effects of cadmium. Recent data from the National Clearinghouse for Smoking and Health (1975) provide a quantitative picture of the numbers of individuals as a function of age and sex who are smokers in the United States. Among adults over 20 years of age, 34 percent are smokers (46.9 million people) of whom 25.9 million are males. Average cigarettes consumed daily by men and women are 23 and 19 cigarettes daily. Of teenagers (13-19 years old), there are 6 million smokers, with increases in this number presently being seen. Thus, a large segment of the present U.S. population could be expected to be at potential increased risk for adverse health effects of cadmium, especially those smokers residing in the vicinity of high cadmium emitting point sources.

Also of special interest are the numbers of children in various urban areas who may be at increased risk to cadmium exposure, and Table 4-23 presents natality data for 1970 and 1975 as provided by the National Center for Health Statistics (1975, 1978). As noted earlier, children are clearly at risk for


1
2
3
4
5
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7
8
9
1. NORTHEAST
2. MID-ATLANTIC
3. SOUTH ATLANTIC
4. EAST NORTH CENTRAL
5. EAST SOUTH CENTRAL
6. WEST NORTH CENTRAL
7. WEST SOUTH CENTRAL
8. MOUNTAIN
9. PACIFIC

Figure 4-6. Regions used in cadmium analysis.

Source: Coleman (1977).

TABLE 4-23. NUMBER OF BIRTHS BY RACE AND SIZE OF POPULATION

Urban areas by population size	Births, 1970[a]			
	White	Black	Other	Total
≥100,000	772,230	321,412	24,394	1,118,036
50-99,999	286,706	37,024	4,182	327,912
10-49,999	600,166	65,790	10,394	676,350
≥9,999	1,432,162	148,136	28,790	1,609,088
Total	3,091,264	572,362	67,760	3,731,386

Urban areas by population size	Births, 1975			
	White	Black	Other	Total
≥100,000	571,478	276,387	26,332	874,197
50-99,999	222,735	37,885	5,921	266,541
10-49,999	478,382	64,481	13,039	555,902
≤9,999	1,279,401	132,828	35,329	1,447,558
Total	2,551,996	511,581	80,621	3,144,198

[a] Vital Statistics of the United States.
National Center for Health Statistics, DHEW, Washington, DC. 1975

[b] Unpublished data from above.

increased exposure and, possibly, absorption; but they are not necessarily the at special risk for experiencing health effects due to short-term exposure or accumulation of cadmium. However, adverse health effects of cadmium vis-a-vis the population at large typically appear only after many years of low-level chronic exposure. Thus, an argument can be advanced that the segment of the present U.S. population that can most benefit from controlled environmental exposure to cadmium and its associated health effects are the very young.

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Table A-1. AMOUNTS OF MUNICIPAL SEWAGE SLUDGE OF VARYING CADMIUM CONTENT ANNUALLY PRODUCED BY MAJOR U.S. CITIES AND APPLIED TO AGRICULTURAL LAND BY LANDSPREADING*

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
New York, N.Y. (Metropolitan area)		6 - 163	228	Ocean	--	I.D.
Hampstead-Bay Park	1975	70			--	8
Long Beach	1975	18				8
Bowery Bay	1975	47				8
Coney Island	1975	8				"
Humts Point	1975	18				"
Jamaica	1975	4				"
Newton Creek	1975	71				"
Owls Head	1975	18				"
Port Richmaon	1975	3				"
Rockaway	1975	16				"
Tallmans Island	1975	6				"
26th Ward	1975	17				"
Wards Island	1975	6				"
Hampstead-West Long Beach	1975	4				"
Yonkers	1975	163				"
Chicago, Ill.	1976	10 - 210	518	Land application Give away	182[b]	"
North Side	1976	180				4
Calumet	1976	42				"
Hanover Park	1976	10				"
Lemont	1976	16				"
W. Southwest	1976	210				"
Los Angeles, Cal.						I.D.
(City & County)		120	127	Ocean		I.D.
		60	295	Sale for compost		"
Philadelphia, Pa.						
N.E. Plant	1976	90	168	Ocean		4
S.W. & S.E.	1976	25	14	Compost		"
Detroit, Mich.		290	145	Incineration		"

Table A-1 continued. AMOUNTS OF MUNICIPAL SEWAGE SLUDGE OF VARYING CADMIUM CONTENT ANNUALLY PRODUCED BY MAJOR U.S. CITIES AND APPLIED TO AGRICULTURAL LAND BY LANDSPREADING*

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Houston, Tex.	1972-73	112	91	Head dried for		6
North Side	1976	17		brokerage sale		9
Simms	1976	22				I.D.
Baltimore, Md.		25	112	Landfill		4
Back River		7				"
Patapsco		9				"
Dallas, Tex.	1976	59	32	Lagoon		9
Washington, D.C.	1975	22	330	Landfill,		3
			14	Compost		
Cleveland, Ohio						
Southerly		390	114	Landfill		4
Westerly		578				"
Indianapolis, Ind.						
Belmont		240	148	Incineration,		"
Southport		260		Land application		"
Milwaukee, Wis.	1972-73	444	82-171	Miloganite-soil	82	
Jones Island		107		conditioner		6
South Shore		50				4
San Francisco area	1975	15	45	Landfill,		2
			2	Land application		
Boston, MA	1973-75	82	78	Ocean		5
Denver, CO	1972-73	46	64	Land application	64	6
Seattle, WA	1972-73	64	33	Landfill,		
				Soil conditioner		"
Atlanta, GA	1972-73	104	20	Landfill or		
				soil conditioner		"

Table A-1 continued. AMOUNTS OF MUNICIPAL SEWAGE SLUDGE OF VARYING CADMIUM CONTENT ANNUALLY PRODUCED BY MAJOR U.S. CITIES AND APPLIED TO AGRICULTURAL LAND BY LANDSPREADING*

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Newark, NJ	1975	173	104	Incineration		8
Unknown		19	45	Agricultural land	45	I.D.
Miami, FLA	1972-73	149	15	Soil conditioner		6
Tampa, FLA	1975	10	9	Land application		7
Unknown		11	30	Agricultural land	30	I.D.
Little Ferry, NJ	1975	240	38	N.A.		8
Unknown		9	23	Agricultural land	23	I.D.
Unknown		13	23	Agricultural land	23	I.D.
Grand Rapids, MI	Prior to 1974	480	23	N.A.		1
Flint, MI	Prior to 1974	20	23	N.A.		1
Syracuse, NY	1972-73	200	22	Solvay process		6
Madison, WI		73	14	N.A.		4
Unknown		160	18		18	I.D.
Warren, MI	Prior to 1974	110	17	N.A.		1
Unknown		100	14	Agricultural land	14	I.D.
Unknown		5	14	Agricultural land	14	I.D.
Macon, GA	1976	6	15	Land application	15	10
Elizabeth, NJ	1975	72	25			8

Table A-1 continued. AMOUNTS OF MUNICIPAL SEWAGE SLUDGE OF VARYING CADMIUM CONTENT ANNUALLY PRODUCED BY MAJOR U.S. CITIES AND APPLIED TO AGRICULTURAL LAND BY LANDSPREADING*

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Camden, NJ		601	14	Ocean		4
Springfield, MO	1976	54	13	Land application	13	10
Saginaw, MI	Prior to 1974	48	11	N.A.		1
Pontiac, MI	Prior to 1974	12	9	N.A.		"
Kalamazoo, MI	Prior to 1974	12	9	N.A.		"
Ann Arbor, MI	Prior to 1974	4	9	N.A.		"
Unknown		10	9	Agricultural land	9	I.D.
Unknown		269	9	Agricultural land	9	I.D.
Anderson, IN	1972-74	170	9	Land application	9	11
Unknown		176	8	Agricultural land	8	I.D.
Unknown		17	8	Agricultural land	8	I.D.
Kokomo, IN	1972-74	806	7	Lagoon		"
Wyoming, MI		14	6	N.A.		1
Bay City, MI	Prior to 1974	80	6	N.A.		"
Jackson, MI	Prior to 1974	520	5	N.A.		"
Unknown		7	5	Agricultural land	5	I.D.
Danville, VA	1976	18	5	Agricultural land	5	10
Muskegon, MI	Prior to 1974	166	5	N.A.		1

Table A-1 continued. AMOUNTS OF MUNICIPAL SEWAGE SLUDGE OF VARYING CADMIUM CONTENT ANNUALLY PRODUCED BY MAJOR U.S. CITIES AND APPLIED TO AGRICULTURAL LAND BY LANDSPREADING*

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Linden, NJ	1975	65	10	N.A.		8
Battle Creek, MI	Prior to 1974	8	5	N.A.		1
Unknown		683	5	Agricultural land	5	I.D.
Unknown		95	5	Agricultural land	5	I.D.
Unknown		16	5	Agricultural land	5	I.D.
Port Huron, MI	Prior to 1974	8	4	N.A.		1
East Lansing, MI	Prior to 1974	6	4	N.A.		"
Unknown	Prior to 1974	4	4	Landfill and agric land	2	"
Ithaca, NY	1972-73	66	4	Soil conditioner		6
Easton, PA		16	4	Land application		I.D.
Midland, MI	Prior to 1974	10	4	N.A.		1
Unknown		61	4	Agricultural land	4	I.D.
Unknown		38	4	Agricultural land	4	I.D.
Unknown		11	4	Agricultural land	4	I.D.
Columbus, IN	1976	2	3	Land application	3	10
Holland, MI	Prior to 1974	10	3	N.A.	3	1
Ypsilanti, MI	Prior to 1974	166	3	N.A.		"
Sayreville, NJ	1975	39	61	N.A.		3

Table A-1 continued. AMOUNTS OF MUNICIPAL SEWAGE SLUDGE OF VARYING CADMIUM CONTENT ANNUALLY PRODUCED BY MAJOR U.S. CITIES AND APPLIED TO AGRICULTURAL LAND BY LANDSPREADING*

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Unknown		12	3	Agricultural land	3	I.D.
Hopkinville, IN	1976	18	3	Agricultural land	3	10
Xenia, OH	1976	80	3	Land application	3	10
Unknown		7	3	Agricultural land	3	I.D.
Monroe, MI	Prior to 1974	8	3	N.A.		1
Unknown		10	3	Agricultural land	3	I.D.
Marquette, MI	Prior to 1974	2	3	N.A.		1
Muskegon Heights, MI	Prior to 1974	150	3	N.A.		"
Mt. Clemons, MI	Prior to 1974	12	3	N.A.		"
Trenton, MI	Prior to 1974	8	3	N.A.		"
Sault Ste. Marie, MI	Prior to 1974	2	2	N.A.		"
Logansport, IN	1972-74	663	3	Land application		11
Traverse City, MI	Prior to 1974	10	2	N.A.		1
Adrian, MI	Prior to 1974	260	2	N.A.		"
Owosso, MI	Prior to 1974	1,100	2	N.A.		"
Mt. Pleasant, MI	Prior to 1974	14	2	N.A.		"
Benton Harbor, MI	Prior to 1974	220	2	N.A.		"
Escanaba, MI	Prior to 1974	10	2	N.A.		"

Table A-1 continued. AMOUNTS OF MUNICIPAL SEWAGE SLUDGE OF VARYING CADMIUM CONTENT ANNUALLY PRODUCED BY MAJOR U.S. CITIES AND APPLIED TO AGRICULTURAL LAND BY LANDSPREADING*

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Dixon, IL	1976	16	2	Land application	2	10
Frankfort, IN	1976	3,171	2	Land application	2	"
Las Virgenes CA	1976	5	2	Land application	2	"
Unknown		8	2	Agricultural land	2	I.D.
Peru, IN	1972-74	164	2	Land application		11
Crawfordsville, IN	1972-74	15	2	Land application		11
Unknown		168	2	Agricultural land	2	I.D.
Iron Mountain, MI	Prior to 1974	6	2	N.A.		1
Albion, MI	Prior to 1974	48	2	Agricultural land	2	"
Unknown		16	2	Agricultural land	2	I.D.
Unknown		9	2	Agricultural land	2	I.D.
Unknown		19	2	Agricultural land	2	I.D.
Niles, MI	Prior to 1974	14	2	N.A.		1
Grand Haven, MI	Prior to 1974	14	2	N.A.		"
Menominee, MI	Prior to 1974	4	1	N.A.		"
Cadillac, MI	Prior to 1974	36	1	N.A.		"
Lebanon, IN	1972-74	40	1	Agricultural land	1	11
Noblesville, IN	1972-74	12	1	Land application		"

Table A-1 continued. AMOUNTS OF MUNICIPAL SEWAGE SLUDGE OF VARYING CADMIUM CONTENT ANNUALLY PRODUCED BY MAJOR U.S. CITIES AND APPLIED TO AGRICULTURAL LAND BY LANDSPREADING*

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Marshall, MO	1976	16	1	Land application	1	10
Wilmington, OH	1976	15	1	Agricultural land	1	"
Unknown		7	1	Agricultural land	1	I.D.
Unknown		1	1	Agricultural land	1	I.D.
Charlotte, MI	Prior to 1974	14	1	N.A.		1
Ironwood, MI	Prior to 1974	4	1	N.A.		"
Hancock, MI	Prior to 1974	4	1	N.A.		"
Three Rivers MI	Prior to 1974	44	1	N.A.		"
Chippewa Falls, WI	1976	7	1	Land application	1	10
Litchfield, IL	1976	6	1	Land application	1	"
Kendallville, IN	1976	28	1	Land application	1	"
Unknown		22	1	Agricultural land	1	I.D.
Unknown		18	1	Agricultural land	1	I.D.
Unknown		970	1	Agricultural land	1	I.D.
Unknown		16	1	Agricultural land	1	I.D.
Marshall, MI	1976	16	1	N.A.		10
Gladstone, MI	Prior to 1974	4	1	N.A.		1
Howell, MI	Prior to 1974	18	1	N.A.		1

Table A-1 continued. AMOUNTS OF MUNICIPAL SEWAGE SLUDGE OF VARYING CADMIUM CONTENT ANNUALLY PRODUCED BY MAJOR U.S. CITIES AND APPLIED TO AGRICULTURAL LAND BY LANDSPREADING*

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Manistique, MI	Prior to 1974	4	1	N.A.		"
Tipton, IN	1972-74	11	1	Land application		11
Unknown		10	0.5	Agricultural land	0.5	I.D.
Unknown		9	0.5	Agricultural land	0.5	I.D.
Milford, MI	Prior to 1974	2	0.5	N.A.		1
Essexville, MI	Prior to 1974	4	0.5	N.A.		"
Norway, MI	Prior to 1974	2	0.5	N.A.		"
St. Ignance, MI	Prior to 1974	4	0.5	N.A.		"
Unknown		7	0.5	Agricultural land	0.5	I.D.
Unknown		23	0.5	Agricultural land	0.5	I.D.
Unknown		8	0.5	Agricultural land	0.5	I.D.
Constantine, MI	Prior to 1974	16	0.5	N.A.		1
Dexter, MI	Prior to 1974	36	0.5	N.A.		"
Lanse, MI	Prior to 1974	8	15	N.A.		"
Unknown		13	0.3	Agricultural land	0.3	I.D.

Table A-1 continued. AMOUNTS OF MUNICIPAL SEWAGE SLUDGE OF VARYING CADMIUM CONTENT ANNUALLY PRODUCED BY MAJOR U.S. CITIES AND APPLIED TO AGRICULTURAL LAND BY LANDSPREADING*

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
TOTAL Named Cities (N = 61)	2 - 3,171	2 - 3,171	3,423		391	
TOTAL Unknown Cities (N = 40)	1 - 970	1 - 970	283		281	
TOTAL CITIES (N = 101)	1 - 371	1 - 371	3,706 3,706 = 30% of sludge generated in U.S.		672 672 = 25% of sludge agriculturally landspread	

[a] Sources of Information:

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11. Sommers, L. E., D. W. Nelson, and K. J. Yost. 1976. Variable Nature of Chemical Composition of Sewage Sludges. Journal of Environmental Quality. 5(3).

I.D.: Impact of Annual Cadmium Application Rates on Current Municipal Sludge Landspreading Practices, EPA, 1978.

[b] Chicago is planning to landspread by opting for the "crop monitoring" approach allowed under proposed sludge criteria (Federal Register, Monday, February 6, 1978, Part II, Vol 43, No. 25; Pg. 4954 - 4955).